MEDICINE

Prep Manual for Undergraduates

## Fifth Edition

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Contents

Chapter 1

Diseases of Blood

Q. Give a brief account of erythropoietin (EPO), recombinant human erythropoietin (rHuEPO) and darbepoietin alpha.

Q. What are the ectopic sources of erythropoietin?

- Erythropoietin (EPO) is a glycoprotein having a molecular weight of 36,000 Dalton. It is primarily produced by the juxtatubular interstitial cells of the renal cortex. In foetus, liver is the primary site of production of EPO.
- Hypoxia is the most potent stimulus for EPO production. Kidneys respond to hypoxia by increased production of EPO. Another important stimulant is the presence of anaemia.
- EPO stimulates erythropoiesis by acting on the erythropoietic stem cells, stimulating increased proliferation. It may also protect neuronal cells from noxious stimuli.

Hypoxia → Kidneys → Erythropoietin → Erythropoiesis ↑ → Haemoglobin ↑ → Reduction in hypoxia
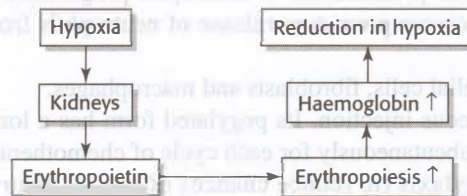
Ectopic Sources of EPO

- Polycystic kidneys.
- Cerebellar haemangioblastoma.
- Uterine fibroma.
- Renal carcinoma.
- Hepatoma.
- Phaeochromocytoma.

Recombinant Human Erythropoietin (rHuEPO)

- It has the same biological effects as endogenous erythropoietin.
- Available as erythropoietin-α and erythropoietin-β.
- Recommended in the treatment of anaemia associated with chronic renal failure. (Patients with normal or low iron stores need concomitant administration of iron to achieve an optimal erythropoietic response).
- Other possible indications include anaemia of chronic inflammation and anaemia (haemoglobin <10 g/dL) in patients with cancer given chemotherapy without curative intent. It is not indicated in patients with cancer who are not being treated with chemotherapy.
- Also useful for treating zidovudine-induced anaemia in HIV patients, and for the treatment of anaemic patients (haemoglobin >10 to ≤13 g/dL) who are at high risk for peri-operative blood loss from elective, non-cardiac, non-vascular surgery to reduce the need for allogeneic blood transfusions.
- Side effects include hypertension, bleeding, increased risk of thrombosis, headache, arthralgia, nausea, oedema, diarrhoea and progression of cancers.

Darbepoetin Alpha

- An erythropoiesis stimulating protein similar to EPO.
- Produced in Chinese hamster ovary cells by recombinant DNA technology.

- Half-life approximately three times rHuEPO and hence needs to be given less frequently.
- Side-effect profile and therapeutic value similar to rHuEPO; not approved for zidovudine-induced anaemia and for peri-operative blood loss.

Q. Discuss briefly about haematopoietic growth factors.

- Haematopoietic growth factors (HGFs) act at different stages of haematopoietic cell differentiation.
- Some HGFs such as interleukin (IL)-1, IL-3, IL-6 exert their primary effects early in stem cell differentiation and are therefore important for the differentiation of multiple blood lineages.
- Others such as EPO, granulocyte colony-stimulating factor (G-CSF), granulocyte–macrophage colony-stimulating factor (GM-CSF) and thrombopoietin (TPO) exert their effects later in the differentiation cascade, and their effects are more lineage specific. Their recombinant forms are available for therapeutic use.

Erythropoietin

- Discussed above.

G-CSF

- Promotes the survival, stimulates the proliferation of neutrophil progenitors and promotes their differentiation into mature neutrophils. In addition, it causes premature release of neutrophils from the bone marrow and enhances their phagocytic function.
- Normally it is produced by endothelial cells, fibroblasts and macrophages.
- Dose is 5 μg/kg daily as subcutaneous injection. Its pegylated form has a long duration of action and requires to be given as a one-time dose of 6 mg subcutaneously for each cycle of chemotherapy.
- Recommended for primary prophylaxis (to reduce chances of febrile neutropenia following chemotherapy) only if the risk of febrile neutropenia is high (>20%) as determined by disease characteristics and myelotoxicity of drugs used. For patients receiving chemotherapeutic regimens who have an intermediate risk of febrile neutropenia (10 to 20%), age >65 years, coexisting illnesses and poor performance status, prophylactic use of G-CSF is indicated.
- Recommended for primary prophylaxis after autologous stem cell transplantation. However, not recommended after allogeneic stem-cell transplantation because of increased risks of severe graft-versus-host disease and transplantation-related death.
- Also recommended for secondary prophylaxis in patients with solid tumours with a previous history of febrile neutropenia who require high-dose chemotherapy and any dose reduction may compromise treatment outcome (e.g., patients with estrogen-receptor-negative breast cancer or non-Hodgkin's lymphoma). If further infections in the next treatment cycle are considered life threatening, G-CSF may be used.
- It is not routinely recommended in all patients with neutropenia and fever. However, it may be administered in patients who have high risk of infection-related complications, prolonged (>10 days) and severe neutropenia (<100/μL), hypotension, multiorgan dysfunction or invasive fungal infection.
- It is not recommended in neutropenic patients who are afebrile.
- Both G-CSF and GM-CSF have been used successfully in mobilising stem cells from bone marrow for stem cell transplantation.
- The use of G-CSF in patients undergoing chemotherapy for breast carcinoma may predispose the patient to acute myeloid leukaemia or myelodysplastic syndrome. However, the benefit of using growth factors outweighs possible risks.
- Adverse effects include fever, and bone and joint pains.

GM-CSF

- It causes an increase in neutrophil, eosinophil, macrophage and sometimes lymphocyte counts.
- Usually administered as a daily subcutaneous injection of 250 μg/m^2.
- Both G-CSF and GM-CSF appear to have similar efficacy in the indications given above.

TPO

- It is the most potent cytokine promoting proliferation and maturation of megakaryocytes. It also primes the platelets to aggregate in response to subthreshold levels of thrombin, collagen and adenosine diphosphate (ADP).
- Normally produced by liver, skeletal muscles and kidneys.
- In cancer patients receiving chemotherapy, it has been shown to reduce the duration of post-chemotherapy thrombocytopenia, though there is no increase in survival.
- However, many patients produce antibodies against TPO and these antibodies also cross-react with and neutralize endogenous thrombopoietin to produce a paradoxical thrombocytopenia.
- Two TPO-receptor agonists for refractory ITP patients: eltrombopag and romiplostim

Q. Define eosinophilia. What are the common causes of eosinophilia?

- Eosinophilia is an absolute eosinophil count exceeding $500/\mu L$. Common causes of eosinophilia are the following:

• Helminthic infestations	• Drugs	• Collagen vascular diseases
• Loeffler's syndrome	• Sulphonamides	• Rheumatoid arthritis
• Tropical eosinophilia	• Aspirin	• Churg–Strauss syndrome
• Allergic conditions	• Nitrofurantoin	• Malignancies
• Hay fever	• Penicillins	• Hodgkin's lymphoma
• Asthma (including allergic bronchopulmonary asper-gillosis)	• Cephalosporins	• Chronic myeloid leukaemia
	• Allopurinol	• Solid organ cancers
• Serum sickness	• Carbamazepine	• Eosinophilic leukaemia
		• Idiopathic hypereosinophilic syndrome

Q. Discuss the abnormalities that can be seen on a peripheral blood smear examination.

Anisocytosis

- Variations in the size of red blood cells.
- Seen in iron deficient anaemia, megaloblastic anaemia, moderate or severe thalassemia, post transfusion and sideroblastic anaemia.

Poikilocytosis

- Variations in the shape of red blood cells.
- Seen in iron deficient anaemia, thalassaemia and sideroblastic anaemia.

Microcytosis

- Red blood cells smaller than their normal size (<75 fL).
- Seen in iron deficient anaemia, thalassaemia and sideroblastic anaemia.

Macrocytosis

- Red blood cells larger than 100 fL.
- Seen in vitamin B_{12} and folic acid deficiency.

Hypochromia

- Red cells having lower haemoglobin as judged by their appearance under microscopy. The central pallor is more than one-third the diameter of red cell.
- Seen in iron deficient anaemia, thalassaemia and sideroblastic anaemia.

Polychromasia

- Red blood cells show colour variability; some (usually the majority) are usual red color, while others are bluish.
- Associated with reticulocytosis.

Basophilic Stippling or Punctate Basophilia

- Presence of scattered deep blue dots in the cytoplasm of red blood cells with Romanowsky staining. These represent altered ribosomes.
- Seen in pathologically damaged young red cells.
- Also seen in severe anaemia, β-thalassaemia and chronic lead poisoning.

Target Cells

- Flat red cells with a central mass of haemoglobin (dense area), surrounded by a ring of pallor (pale area) and an outer ring of haemoglobin (dense area).
- Seen in chronic liver diseases, hyposplenism and haemoglobinopathies.

Howell–Jolly Bodies

- These are remnants of nuclear material left in the erythrocyte after the nucleus is extruded. They are normally removed by the spleen.
- Appear as solitary round mass, relatively large within haemoglobinized portion of red blood cell; on Wright's stain, appear dark blue or purple.
- Seen in non-functioning or absent spleen and megaloblastic anaemias.

Heinz's Bodies (Ehrlich's Bodies)

- Formed from denatured aggregated haemoglobin.
- A submembranous small round mass in red cells seen on supravital stain; not seen with routinely stained film.
- Seen in thalassaemia, haemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficiency, asplenia and chronic liver disease.

Acanthocytes or Spur Cells

- Red blood cells showing irregular spicules.
- Seen in abetalipoproteinaemia, advanced liver disease, and hyposplenism.

Burr Cells

- Red blood cells showing regularly placed spicules.
- Seen in uraemia, and post transfusion.

Schistocytes

- These are fragmented red cells (with central pallor often missing) and are seen in intravascular haemolysis.

Spherocytes

- These are small, densely packed red cells with loss of central pallor and occur in hereditary spherocytosis and immuno-haemolytic anaemias.

Microspherocytes

- Red blood cells are both hyperchromic and significantly reduced in size and diameter; occur in low numbers in patients with a spherocytic haemolytic anaemia. Typical of burns and of microangiopathic haemolytic anaemia.

Q.   Describe various blood indices used in patients with anaemia.

- **Mean corpuscular volume (MCV)**
  Haematocrit × 10/RBC count × 106 (normal range 90 ± 8 fL; fL stands for femtolitres)
- **Mean corpuscular haemoglobin (MCH)**
  Haemoglobin (g/dL) ×10/RBC count × 10^6 (normal range 30 ± 3 pg)
- **Mean corpuscular haemoglobin concentration (MCHC)**
  Haemoglobin (g/dL) × 10/haematocrit (normal range 33 ± 2%)
- **Red blood cell count**
  Males 4.5–5.5 × 10^6/mm³; Females 4–4.5 × 10^6/mm³
- **Reticulocyte count**
  Expressed as percent of red blood cell count (normal < 2.5%)
- **Corrected reticulocyte count (to adjust for severity of anaemia)**
  Expressed as % reticulocyte count × observed haematocrit/normal haematocrit
- **Reticulocyte index**
  Expressed as % reticulocyte count × observed haematocrit/normal haematocrit × ½ (multiplication by
  ½ is to account for premature release of reticulocytes from bone marrow in anaemia)
- **Red cell distribution width (RDW)**
  (Standard deviation of red cell volume + mean cell volume) × 100 (normal 11–16) (an index of variation
  in cell volume within the red cell population)
  Increased in iron-deficiency anaemia and megaloblastic anaemia
  Normal in thalassaemias, anaemia of chronic disease and bone marrow aplasia

Q.   Discuss the aetiology, classification, clinical features and general management of anaemia.

Definition

- Anaemia is defined as a state in which the blood haemoglobin level is below the normal range for the patient's age, sex
  and altitude of residence.
- Normal adult haemoglobin level lies between 13–16 g/dL in males and 11.5–15.0 g/dL in females.

Classification

- Anaemias can be classified in two ways:
  1. Based on the cause of anaemia.
  2. Based on the morphology of red cells.

Based on the cause of anaemia	Based on the morphology of red cells

- Blood loss, which may be acute or chronic
  - Acute (large volume over short period)
  - Chronic (small volume over long period)
- Inadequate production of normal red cells
- Excessive destruction of red cells
	- Normocytic
	- Microcytic
	- Macrocytic

Aetiology

Due to blood loss	
- Acute blood loss	Trauma, post-partum bleeding
- Chronic blood loss	Hook worms, bleeding peptic ulcer, haemorrhoids, excessive menstrual loss

Due to inadequate production of normal red cells	
● Deficiency	Iron, vitamin B_{12}, folate
● Toxic factors	Chronic inflammatory and infective diseases, renal failure, hepatic failure, drugs leading to aplastic anaemia
● Endocrine deficiency	Hypothyroidism, hypoadrenalism, reduced EPO due to renal failure, hypogonadism, hypopituitarism
● Marrow invasion	Leukaemias, fibrosis, secondary carcinoma
● Marrow failure	Hypoplastic, aplastic anaemia
● Maldevelopment	Sideroblastic anaemia, haemoglobinopathies like sickle cell disease and thalassaemias, neoplastic disorders of erythropoiesis

Due to excessive destruction of red cells (Haemolytic anaemias)	
● Genetic disorders	Red cell membrane, haemoglobin or enzyme abnormalities
● Acquired disorders	Immune, toxic, mechanical and infectious causes

Clinical Features

Symptoms

- Fatigue, lassitude, dyspnoea, palpitation.
- Dizziness, headache, syncope, tinnitus, vertigo.
- Irritability, sleep disturbances, lack of concentration.
- Throbbing in head and ears, paraesthesia in fingers and toes.
- Anorexia, indigestion, nausea, bowel disturbances.
- Angina, intermittent claudication, transient cerebral ischaemia.
- Symptoms of cardiac failure.
- Amenorrhoea, polymenorrhoea.

Signs

- Pallor of skin, palms, oral mucous membrane, nail beds and palpebral conjunctivae. The palmar creases become as pale as the surrounding skin when the haemoglobin is below 7 g/dL.
- Tachycardia, wide pulse pressure.
- Oedema.
- Cervical venous hum, hyperdynamic precordium.
- Ejection systolic murmur, best heard over the pulmonary area.
- Cardiac dilatation and later signs of cardiac failure.

Signs Suggesting a Specific Aetiology of Anaemia

● Jaundice	Haemolytic anaemia, chronic hepatitis, megaloblastic anaemia
● Angular cheilitis	Iron-deficiency anaemia
● Glossitis	Iron-deficiency anaemia, vitamin B_{12} deficiency, folate deficiency
● Splenomegaly	Malaria, chronic haemolytic anaemia, acute infection, leukaemia, lymphoma, portal hypertension vitamin B_{12} deficiency
● Frontal bossing	Chronic haemolytic anaemia
● Neurological changes (dementia, ataxia)	Vitamin B_{12} deficiency

Approach to Diagnosis of Cause of Anaemia

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                              │ Anaemia  │
                              └────┬─────┘
                                   │
        ┌──────────────────┐   ┌──────┐   ┌──────────────────────────────┐  yes  ┌────────────────────┐
        │Reticulocyte count├──►│ High ├──►│↑ bilirubin, ↓ haptoglobin, ↑ LDH├─────►│ Haemolytic anaemia │
        └────────┬─────────┘   └──────┘   └──────────────┬───────────────┘       └─────────┬──────────┘
                 │                                        │ No                              │
        ┌────────▼─────────┐                      ┌───────▼────────┐              ┌─────────▼──────────┐
        │  Normal or low   │                      │ Acute blood loss│             │   Coombs' test     │
        └────────┬─────────┘                      └────────────────┘              └─────────┬──────────┘
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        ┌────────▼─────────┐                                        ┌───────▼──────┐              ┌─────────▼─────────┐
        │   Check MCV,     │                                        │   Positive   │              │     Negative      │
        │ peripheral smear │                                        └───────┬──────┘              └─────────┬─────────┘
        └────────┬─────────┘                                        ┌───────▼──────┐              ┌─────────▼─────────┐
                 │                                                  │     AIHA     │              │    Congenital     │
                 │                                                  └──────────────┘              │    haemolytic     │
                 │                                                                                │     anaemia       │
                 │                                                                                └───────────────────┘
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| Microcytic | Normocytic | Macrocytic |

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┌──────────┐              ┌────────────┐                    ┌──────────────────────┐
│ Microcytic│             │ Normocytic │                    │     Macrocytic       │
└────┬─────┘              └─────┬──────┘                    └──────────┬───────────┘
     │                          │                                      │
┌────▼─────┐  ┌────────────┐ ┌──▼──────────┐               ┌──────────▼───────────┐
│Low ferritin│ │Normal ferritin│ │Pancytopenia │            │ Check B₁₂ and folate │
└────┬─────┘  └──────┬─────┘ └──┬───────┬──┘                └──────────┬───────────┘
     │               │     yes  │       │ No            ┌──────────────┴────────────┐
┌────▼─┐      ┌──────▼──────┐ ┌─▼────────────────┐ ┌────▼─────┐            ┌────────▼────────┐
│ IDA  │      │Hb electrophoresis│ │Aplastic anaemia │ │Creatinine│ ┌──────┐ │Normal  │       │ Low │
└────┬─┘      └──────┬──────┘ │Myelophthisic anaemia│ └──┬───┬──┘ │Normal│ └────────┘       └──┬──┘
     │               │        │Leukaemia           │    │   │  ┌──┴───┐                         │
┌────▼────┐   ┌──────▼──────┐ └──────────────────┘  Normal Elevated                    ┌────────▼────────┐
│↑HbA2,HbF│   │   Normal    │                         │   └──────┐                     │  Folate/B₁₂     │
└────┬────┘   └──────┬──────┘                         │ TSH       │                     │  deficiency     │
     │               │                                │    ┌──────▼──────┐              └─────────────────┘
┌────▼─────┐  ┌──────▼──────────┐                     │    │Anaemia of CKD│
│Thalassaemia│ │      ACD        │              ┌──────▼──┐ └─────────────┘
└──────────┘  │Siderblastic anaemia│            │ Normal  │         │High│
              │ (Bone morrow    │              └────┬────┘         └──┬─┘
              │ to differentiate)│                   │                │
              └─────────────────┘              ┌─────▼──┐  ┌───────────▼──────────┐
                                               │Serum   │  │   Hypothyroidism     │
                                               │electrophoresis│ └──────────────────┘
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MCV = mean corpuscular volume; AIHA = Autoimmune haemolytic anaemia; IDA = Iron deficiency anaemia;
ACD = Anaemia of chronic disease; TSH = Thyroid stimulating hormone; CKD = Chronic kidney disease;
LFT = Liver function tests; MDS = Myelodysplastic syndrome

General Management

- Blood transfusion.
  - In significantly symptomatic and severely anaemic patients.
  - Packed cells are preferred.
  - Care has to be taken to avoid circulatory overloading, especially in elderly patients. Intravenous frusemide 20 mg may be given prior to transfusion.
- Prompt treatment of infections and cardiac failure.

Q. Give a brief description about the anaemias due to blood loss.

- Anaemias due to blood loss could be acute (large volume over short period) or chronic (small volume over long period).

Anaemias Due to Acute Blood Loss

- A healthy adult can lose about 500 mL of whole blood without any ill effect, e.g. blood donation. When more is lost, compensatory mechanisms come into operation. The blood flow to skin and skeletal muscle is reduced, conserving the blood flow to vital organs like brain, kidney and heart. With continued blood loss, these compensatory mechanisms fail.

Clinical Features

- In the initial stages, pulse rate rises and blood pressure is maintained. Patient is pale, cold and sweating.
- If bleeding gets arrested, production of plasma replenishes the volume loss, resulting in dilution of remaining red cells. Anaemia appears in 24–36 hours. This anaemia gets corrected in a few weeks, provided body iron stores are not depleted.
- If bleeding continues, compensatory mechanisms fail and hypovolaemic shock ensues, which may result in death.

> Earliest signs to look for in a patient with suspected blood loss (especially internal bleeding) are postural hypotension and tachycardia.

Investigations

- Haemoglobin and haematocrit are normal in early stages (before haemodilution).
- Anaemia (haemoglobin and haematocrit drop) develops in 24–36 hours due to haemodilution.
- A transient leucoerythroblastic blood picture may be seen in very early stages.
- Reticulocytosis occurs at a later stage.

Treatment

- If symptomatic replace the blood loss by transfusion of whole blood or packed cells.

Anaemia of Chronic Blood Loss

- Compensatory mechanisms replenish the plasma volume and red cell loss. But, if the blood loss continues, body iron stores are depleted and anaemia due to iron deficiency appears.

Q. Discuss the aetiology, clinical manifestations, diagnosis and management of iron deficiency anaemia.

Q. Write a short note on Plummer–Vinson syndrome (sideropenic dysphagia; Patterson–Kelly syndrome).

- Iron deficiency is the most common cause of anaemia.
- Daily iron requirement is 10–15 mg, of which nearly 10% is absorbed in males and 15% in females.
- Children who consume large amounts of cow milk are particularly prone to iron deficiency:
  - Cow's milk iron poorly absorbed
  - Calcium present in milk inhibits iron absorption
  - Cow's milk may cause protein allergy with GI bleeding (occult or gross).

- Approximately 20 mL of senescent red cells are cleared daily, and the 20 mg of iron in those cells is recycled for the production of new red cells.
- Post-partum, iron is lost as lactoferrin in breast milk. However, these losses are balanced by absence of menstruation in the lactating woman.

Aetiology (causes of iron deficiency)

• Physiological	Post-natal growth spurt, adolescent growth spurt, menstruation, pregnancy
• Iron loss	Hook worm infestation, schistosomiasis, menorrhagia, post-partum haem-orrhage, peptic ulcer, piles, neoplastic diseases, gastric erosions from anti-inflammatory drugs, malaria (intravascular haemolysis with subsequent loss of haemoglobin iron in urine; also suppresses erythropoiesis)
• Inadequate diet	Includes excessive consumption of cow milk in children
• Malabsorption (reduced iron absorption)	Inflammatory bowel disease, post-gastrectomy, coeliac disease, autoimmune gastric atrophy, *Helicobacter pylori* gastritis

- Iron-deficiency anaemia without other clinical clues of intestinal malabsorption is one of the most common extraintestinal manifestations of coeliac disease.

Clinical Features

- Clinical features of iron-deficiency anaemia include the general symptoms and signs of anaemia (refer back).
- Characteristic features of iron deficiency include the following:
  - Angular stomatitis
  - Glossitis
  - Brittle fingernails, platonychia, koilonychia
  - Pica indicates a craving for non-nutritive and strange items like coal, earth (geophagia), tomatoes, greens, starch and ice (pagophagia).
- Restless leg syndrome (compulsion to move limbs while at rest) may occur due to reduced brain iron levels
- Iron-deficiency during pregnancy may reduce foetal brain maturation, cognitive defects in child and maternal depression
- Plummer–Vinson syndrome (sideropenic dysphagia; Patterson–Kelly syndrome) occurs in long-standing iron deficiency. The characteristic features are:
  - Iron deficiency anaemia.
  - Glossitis.
  - Koilonychia.
  - Post-cricoid web resulting in dysphagia. The dysphagia is intermittent and is more for solids than liquids. The post-cricoid web can be demonstrated endoscopically or by barium swallow. May also be due to weakened oesophageal muscle contractions.
  - Increased risk of squamous-cell carcinoma of pharynx and oesophagus.
  - Treatment of Plummer–Vinson syndrome is with iron. Dilatation of web in case of severe obstruction may be required.
  - Upper GI endoscopy may be required every year for the early diagnosis of cancers.

Investigations

- To confirm iron-deficiency anaemia.
- To determine the cause of iron deficiency.

To Confirm Iron Deficiency Anaemia

- Haemoglobin is reduced.
- Mean corpuscular volume (MCV) is reduced (microcytosis) to below 80 fL.
- Peripheral smear study:
  - Microcytosis, and hypochromia.
  - Elliptical cells and poikilocytes are seen in severe cases.

- Reticulocyte count is normal; it is elevated if blood loss is the aetiology and the patient has enough iron stores or is on iron therapy.
- Bone marrow study:
  - Moderate erythroid hyperplasia.
  - Bone marrow iron stores are markedly reduced or absent (Prussian blue staining).
- Plasma iron is reduced and total iron-binding capacity (TIBC) is raised.
- Plasma transferrin saturation is reduced (<10%).
- Serum ferritin level is reduced (normal >100 μg/L).
- Elevated red cell protoporphyrin (normal <30 μg/dL) reflecting the body's inability to complete haem production without iron. Also elevated in lead poisoning.
- Serum soluble transferrin receptor is increased (not so in anaemia of chronic disease). Unlike serum ferritin levels, it is not increased in the presence of inflammation.
- Hepcidin produced by the liver regulates iron concentrations and tissue iron distribution via inhibition of intestinal iron absorption, iron reclamation by macrophages and iron mobilisation from hepatic stores; its production is decreased in iron-deficiency anaemia and increased during inflammation and iron overloading.

Causes of Microcytosis

- Iron deficiency
- Thalassaemia
- Sideroblastic anaemia
- Anaemia of chronic disease (some cases)
- Lead poisoning

To Determine the Cause of Iron Deficiency

- The investigations chosen depend on the age, sex, history and physical findings. In the absence of any clear clue, the following investigations may be done, mainly to check for chronic blood loss from the GI tract.
  - Stool for occult blood and hookworm infestation.
  - Sigmoidoscopy and colonoscopy.
  - Upper gastrointestinal endoscopy.
  - Barium meal and barium enema (less sensitive than colonoscopy and upper GI endoscopy).
  - Investigations may be done for malabsorption if diarrhoea or steatorrhoea present or anaemia is refractory despite iron.
  - Urine for schistosomiasis.

Management

- Treatment of underlying cause.
- Treatment of iron deficiency by oral iron therapy or parenteral iron therapy.

Oral Iron Therapy

- Most patients can be treated with oral iron.
- Commonly used salts of iron include ferrous sulphate, ferrous gluconate, ferrous fumarate and others. Ferrous sulphate tablets contain 30% elemental iron; ferrous gluconate 12% is elemental iron and ferrous fumarate is 33% elemental iron.
- Dose is one tablet two to three times a day. Should not be given with food because phosphates, phytates and tannates in food bind iron and impair its absorption.
- Another form of iron is ferrous ascorbate. Iron absorption is greater as compared to other formulations of iron. Further iron absorption is not inhibited by food intake.
- Some patients develop side effects like dyspepsia, constipation or diarrhoea. This can be relieved by taking iron with food or by changing to a different iron salt or a controlled-release preparation or a liquid preparation.
- Response to oral iron therapy usually appears within 7–10 days. This is in the form of a reticulocyte response, usually not exceeding 10%.
- Failure to respond to oral iron therapy may be due to one or more of the following reasons:
  - Not taking the tables (check for grey or black coloured stools).
  - Continuing blood loss.

- Ingestion of certain drugs along with iron that reduce its absorption (antacids, H_2-receptor blockers, proton-pump inhibitors, tetracyclines).
  - Other complicating conditions.
  - Severe malabsorption.
  - Wrong diagnosis.
- Duration of oral iron therapy:
  - Haemoglobin should return to normal range in 4–6 weeks, and if not, failure of response should be sought.
  - If haemoglobin has returned to normal, oral iron should be continued for at least 6 months or may be 1 year in order to replenish the body iron stores.
  - In those patients whose iron deficiency is recurrent (e.g. malabsorption, deficient intake, continuing blood loss), long-term iron supplements at a minimum dose are required.

Parenteral Iron Therapy

- For parenteral iron therapy, iron-sorbitol, iron sucrose, ferric gluconate or iron-dextran (Imferon) may be used.
- Parenteral iron therapy should be prescribed only if diagnosis of iron deficiency is definite as otherwise therapy might result in iron overload.

Indications of parenteral iron therapy

- Genuine gastrointestinal intolerance to oral iron
- Disorders of GI tract interfering with the absorption of iron, e.g. severe malabsorption
- When the rate of iron (blood) loss exceeds the rate at which iron can be absorbed
- When a gastrointestinal condition may worsen with oral iron (e.g. some cases with ulcerative colitis)
- For correction of severe anaemia associated with rheumatoid arthritis, late pregnancy and following major operations
- Non-compliance
- Anaemia (iron deficiency) associated with chronic renal failure (along with EPO) when oral iron does not produce expected rise in haemoglobin. Also indicated in patients with anaemia and chronic renal failure who are on regular haemodialysis

Calculation of total dose of iron required

Iron needed in mg = (normal haemoglobin – patient's haemoglobin) × weight in kg × 2.21 + 1000
- Normal haemoglobin in males is taken as 14 g/dL and females as 12 g/dL
- The addition of 1000 is to correct the deficit and replenish the body iron stores

Iron-Sorbitol

- Given intramuscularly but never intravenously.
- Recommended dose is 1.5 mg of iron/kg body weight daily, to a maximum of total dose calculated, but not exceeding 2.5 g.

Iron-Dextran (Imferon)

- It may be given intramuscularly but is ideal for intravenous use. Test dose of 5 mg IV over 5 minutes is required before administration of full dose.
- Total iron requirement can be given in one dose.

Intramuscular

- Recommended dose is 100 mg daily until the total required dose is administered or to a maximum of 2 g. It should be administered deep intramuscularly into the buttocks using a "Z-track technique".

Intravenous

- The total dose required is diluted in a solution of isotonic saline and infused slowly.

Iron Sucrose

- Doses of 100–200 mg per day as an IV injection over 3–15 minutes or up to 500 mg over an infusion time of 3 hours.
- Considered to be the safest intravenous preparation of iron.

Ferric Gluconate

- Maximum recommended daily dose is 125 mg IV due to potential for acute adverse reactions.

Toxicity of parenteral iron preparations	
• Pain and swelling at injection site	• Splenomegaly
• Arthralgias	• Aseptic meningitis
• Fever	• Anaphylactic reactions
• Generalised urticarial rash	• Sarcomas at intramuscular injection sites
• Generalised lymphadenopathy	• Haemosiderosis

Q. How will you differentiate various causes of hypochromic microcytic anaemias?

Differential Diagnoses

Laboratory parameters	Iron deficiency anaemia	β-thalassaemia	Anaemia of chronic disease	Sideroblastic anaemia
• Serum iron (normal 60–170 µg/dL)	<30 µg/dL	Normal to high	<50 µg/dL	Normal to high
• TIBC (normal 300–450 µg/dL)	>350 µg/dL	Normal	<300 µg/dL	Normal
• Saturation (%)(normal 20–50%)	<10	30–80	10–20	30–80
• Serum ferritin (normal 15–300 µg/L)	<15 µg/L	50–300 µg/L	30–200 µg/L	50–300 µg/L
• Haemoglobin A_2 (normal <3%)	Reduced	Increased	Normal	Reduced

Q. Give a brief account of sideroblastic anaemias.

- Sideroblastic anaemias are inherited or acquired disorders characterised by refractory anaemia, variable number of hypochromic red cells in peripheral smear and excess of iron and ring sideroblasts in the marrow.

Causes

Hereditary sideroblastic anaemia	Acquired sideroblastic anaemia
• X-linked disorder	• Idiopathic or primary (a type of myelodysplasia)
	• Drugs (e.g. isoniazid, cycloserine, chloramphenicol, busulphan, D-penicillamine)
	• Alcohol abuse
	• Lead toxicity
	• Pyridoxine deficiency
	• Others (rheumatoid arthritis, carcinoma)

Characteristic Features

- Iron overload.
- Characteristic ringed sideroblasts are seen in the bone marrow. The iron-laden mitochondria surround the nucleus and appear as the pathognomonic "rings" with Prussian blue staining.

Other Features

- Bone marrow erythroid hyperplasia and ineffective erythropoiesis.
- Microcytic, and hypochromic red cells on peripheral smear.
- Marked increase in serum iron and transferrin saturation.
- About 10% of the patients with sideroblastic anaemia develop acute myeloblastic leukaemia.

Treatment

- Some patients respond when the drugs, toxins or alcohol are withdrawn.
- In occasional cases, there is a response to pyridoxine or folic acid.
- Otherwise, treatment is supportive with transfusions.

Q. Discuss the aetiology, diagnosis and management of megaloblastic macrocytic anaemias.

Q. Enumerate the causes of macrocytosis.

Megaloblastic Macrocytic Anaemias

- Megaloblasts are abnormal erythroblasts seen in the bone marrow of patients with deficiency of vitamin B_{12}, folate or both. Megaloblasts are abnormally large in size and nucleated. They are well haemoglobinised.
- Macrocytes are erythrocytes with increased MCV. Normal MCV ranges between 80 and 100 femolitres (fL). It is calculated as:

$$MCV \text{ (fL)} = [Haematocrit\ (\%) \times 10]/[RBC\ count\ (10^6/\mu L)]$$

- Hence, the term megaloblastic macrocytic anaemia describes the outstanding feature (increased size of cells) of both the bone marrow and the peripheral blood. Some patients with macrocytosis and anaemia may not have megaloblasts in bone marrow. This is known as non-megaloblastic macrocytic anaemia.
- Megaloblastic anaemias are characterised by macro-ovalocytes and hypersegmented neutrophils, which are absent in non-megaloblastic macrocytic anaemia.

Conditions Resulting in Macrocytosis

• Vitamin B_{12} deficiency	• Liver disease	• Myeloid leukaemia
• Folate deficiency	• Alcohol	• Hypothyroidism
• Antimetabolites (azathioprine, 6-mercaptopurine, 5-fluorouracil, cytosine arabinoside)	• Aplastic anaemia	• Sideroblastic anaemia
	• Myelodysplasia	• Spuriously elevated MCV by automated blood cell counter (hyperglycaemia, marked leucocytosis, cold agglutinins)
• Nitrous oxide abuse	• Acyclovir, zidovudine, stavudine	
	• Trimethoprim, pyrimethamine, metformin, phenytoin	
	• Hydroxyurea	• Pregnancy, newborn (physiological)

Conditions Resulting in Non-Megaloblastic Macrocytic Anaemia

Physiological	Pathological
• Pregnancy	• Alcohol
• Newborn	• Chronic liver disease
	• Hypothyroidism
	• Aplastic anaemia
	• Sideroblastic anaemia
	• Drugs (azathioprine, zidovudine)
	• Myelodysplasia
	• Haemorrhage

Mechanism

- Most megaloblastic macrocytic anaemias are due to a deficiency of vitamin B_{12}, folate or both.
- Both vitamin B_{12} and folate are essential for DNA synthesis. Deficiency of one or both results in failure of DNA synthesis. This results in abnormal cell proliferation. The abnormality in cell proliferation mainly affects haemopoietic tissues (erythrocyte series, granulocyte series and megakaryocyte series) and gastrointestinal epithelial cells.
- Morphological changes in the erythrocyte series in the bone marrow are described as megaloblastic. When DNA synthesis is impaired, cell division is delayed, time between divisions increases, more cell growth occurs and cells become larger in size—"megaloblasts". Synthesis of haemoglobin is unimpaired. The resultant mature erythrocytes derived from these megaloblasts are abnormally large (macrocytes) and abnormal in shape (usually oval) but well haemoglobinised.
- But a large number of these megaloblastic erythroid cells are destroyed in the bone marrow (ineffective erythropoiesis).
  - This results in liberation of large amounts of lactate dehydrogenase (LDH) that rises to high levels in the blood.
- In the bone marrow, abnormal proliferation affecting the granulocyte series results in giant metamyelocytes, and the megakaryocyte series results in dysplastic megakaryocytes.

Diagnosis

- Investigations
  - Haemoglobin is reduced
  - Mean corpuscular volume (MCV) is raised, usually more than 120 fL (macrocytes)
  - RBC count is reduced
  - Reticulocyte count is reduced
  - Total leucocyte count is reduced
  - Platelet count is reduced
  - Peripheral smear study:
    - Oval macrocytosis
    - Poikilocytosis
    - Fragmented red blood cells
    - Hypersegmented neutrophils
  - Indirect bilirubin is mildly elevated (due to increased breakdown of red cells in bone marrow)
- Serum iron is elevated
- Iron-binding capacity is reduced
- Serum ferritin level is increased
- Plasma lactate dehydrogenase is markedly increased
- Bone marrow study:
  - Hypercellular marrow
  - Megaloblastic erythroid cells
  - Giant metamyelocytes
  - Dysplastic megakaryocytes
  - Marrow iron stores increased
- Specific tests for B_{12}/folate deficiency:
  - Reduced serum B_{12}/folate
  - Plasma methylmalonic acid (MMA) elevated (in B_{12} deficiency)
  - Plasma homocysteine elevated
  - Plasma holotranscobalamine II reduced (in B_{12} deficiency)

Management

- Supportive therapy.
- Specific therapy:
  - Treatment of underlying cause of vitamin B_{12} or folate deficiency.
  - Vitamin B_{12} therapy.
  - Folate therapy.

Supportive Therapy

- Blood transfusions should be given in significantly symptomatic and severely anaemic patients. Adequate precautions are to be taken to avoid circulatory overloading, especially in elderly patients. Intravenous frusemide, 20–40 mg may be given prior to transfusion.
- Treatment of infections.
- Treatment of cardiac failure.

Q. Discuss the aetiology, pathogenesis, clinical features, diagnosis and management of Addisonian pernicious anaemia.

- It is a megaloblastic macrocytic anaemia resulting from failure of secretion of intrinsic factor by the stomach not related to total gastrectomy. In the absence of intrinsic factor, dietary vitamin B_{12} is not absorbed and this results in vitamin B_{12} deficiency.

Aetiology

- Autoimmune disease with permanent atrophy of gastric mucous membrane. Immune response is directed against gastric H/K-ATPase, which accounts for associated achlorhydria.
- Long-standing *Helicobacter pylori* infection may play some role in many patients H/K-ATPase.

Pathogenesis

Autoimmune gastric atrophy

↓

Reduced secretion of intrinsic factor

↓

Reduced binding of intrinsic factor to vitamin B_{12} ← Blocking intrinsic factor antibody

↓

Reduced binding of B_{12}-intrinsic factor complex to receptor in ileum ← Precipitating intrinsic factor antibody

↓

Failure of absorption of vitamin B_{12}

↓

Deficiency of vitamin B_{12}

↓

Haemopoietic features | Neurological features | Miscellaneous features

Clinical Features

- Both sexes equally involved.
- Usually occurs between 45 and 65 years of age.
- Higher incidence in people with blood group A.
- Onset and progression are often insidious.
- Clinical features are related to vitamin B_{12} deficiency (see below).
- Hypochlohydria may lead to impaired gastric emptying that may produce dyspepsia, post-prandial fullness and early satiety.
- Many patients have other autoimmune diseases including vitiligo, thyroid diseases, type 1 diabetes mellitus and Addison's disease (occur as part of autoimmune polyglandular endocrinopathy).

Investigations

- Very low serum vitamin B_{12} levels.
- Anti-intrinsic factor antibodies in the serum (in 70% of patients; highly specific). Must be tested >7 days after vitamin B_{12} injection to prevent false positive result.
- Antiparietal cell antibodies (in 85–90%; less specific compared to anti-intrinsic antibodies as also found at low frequency in other autoimmune diseases e.g., Hashimoto's thyroiditis or type 1 diabetes, and in elderly subjects).
- Macrocytic blood picture.
- Megaloblastic bone marrow.
- Abnormal vitamin B_{12} absorption test corrected by addition of intrinsic factor (Schilling test).
- Reticulocyte response to very small doses of parenteral vitamin B_{12}.
- Pentagastrin or histamine-fast achlorhydria.
- Elevated serum gastrin levels.
- Reduced serum pepsinogen I levels.
- Gastric biopsy showing mucosal atrophy.
- Low serum ferritin levels as iron deficiency is often present due to gastric atrophy.

Treatment

- Supportive therapy includes blood transfusion, treatment of infection and physiotherapy in nervous system involvement.
- Vitamin B_{12} therapy:
  - Cyanocobalamin or hydroxocobalamin may be used. Another option is to use methylcobalamin, metabolically active form of vitamin B_{12}.
  - Initial dose of hydroxocobalamin is 1000 μg, deep intramuscularly daily for 1 week.
  - Maintenance dose is 1000 μg of hydroxocobalamin intramuscularly once in a month or 1000 μg of cyanocobalamin once in 3 months indefinitely.
  - An acceptable alternative is to give 1000–2000 μg of vitamin B_{12} orally daily for 1 month followed by 125–500 μg daily indefinitely. Absorption is by passive diffusion.
- Iron therapy with ferrous sulphate 200 mg thrice daily orally should be started soon after the commencement of vitamin B_{12} therapy if the patient has associated iron deficiency (dimorphic anaemia).

Follow-Up

- Clinical and haematological examination once in 6 months.
- Early detection of carcinoma of stomach, which is three times more common in patients with pernicious anaemia. Gastric carcinoid is also more common in these patients as compared to general population.

Q. Write a short note on vitamin B_{12}.

Q. Discuss briefly the causes, manifestations and management of vitamin B_{12} deficiency.

Vitamin B_{12}

- Vitamin B_{12} is essential for normal haemopoiesis and maintenance of normal integrity of the nervous system.
- Vitamin B_{12} (cyanocobalamin) belongs to the family of cobalamins. It is found only in trace amounts in tissues. It has to be converted to a biologically active form before it can be used by tissues. There are two biologically active forms of cobalamins in the body both acting as coenzymes:
  1. Methylcobalamin.
  2. Adenosylcobalamin.
- The main sources of vitamin B_{12} are animal proteins and dairy products. Vegetables contain practically no vitamin B_{12}.
- Vitamin B_{12} is stored in the liver in a quantity sufficient enough to supply for a period of 3 years. Hence, the manifestations of vitamin B_{12} deficiency take at least 3 years to make their appearance.
- Acidic medium of the stomach and pepsin facilitate the breakdown of vitamin B_{12} that is bound to food proteins. The free B_{12} then binds to haptocorrin (HC) released from salivary glands. In small intestine, HC is degraded by pancreatic enzymes and vitamin B_{12} binds to intrinsic factor secreted by gastric parietal cells. This complex is transported to the lower ileum where the complex dissociates and vitamin B_{12} is absorbed by the ileal cells. In plasma, vitamin B_{12} is bound to two proteins, transcobalamin II and HC. Vitamin B_{12} attached to transcobalamin II is known as holotranscobalamin II. It denotes biologically active fraction that is transported to various tissues. Function of HC is not known.
- Normal daily requirement of vitamin B_{12} is 1–2 μg.

Causes

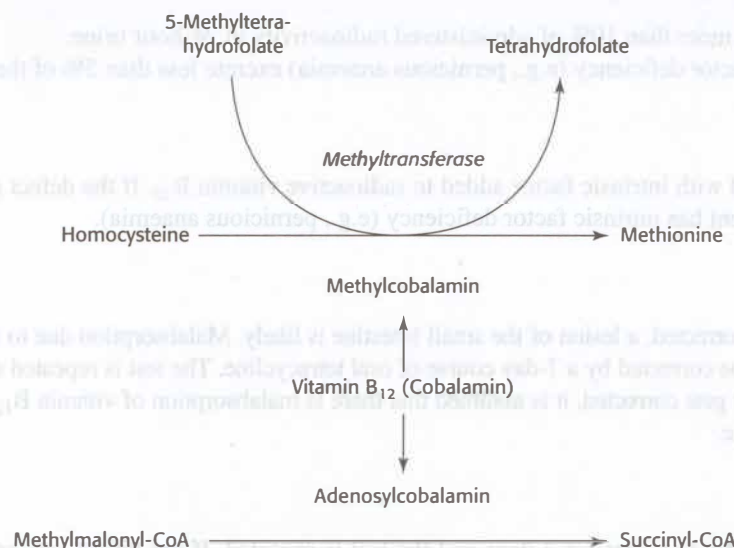| Malabsorption syndromes	Inadequate intake
• Prolonged use of H_2-receptor blockers	• Alcoholics
• Prolonged use of proton-pump inhibitors	• Elderly
• Lack of intrinsic factor (pernicious anaemia, post-gastrectomy, atrophic gastritis)	• Pure vegetarians
• Ileal malabsorption	**Defective transport**
• Crohn's disease	• Transcobalamin II deficiency
• Ileal resection	
• Tropical sprue	
• Bacterial overgrowth	
• Tapeworm infestation	

- Approximately 10–30% of patients on metformin have diminished B_{12} absorption due to calcium-dependent ileal membrane antagonism.
- Nitrous oxide inactivates cobalamin and its use in anaesthesia may precipitate haematologic and neurological deterioration in vitamin B_{12} deficient persons.

Manifestations

Deficiency of vitamin B_{12}

Haemopoietic	Neurological	Miscellaneous
• General symptoms and signs of anaemia • Pallor of skin and mucous membranes • Megaloblastic macrocytic anaemia • Pancytopenia • Splenomegaly	• Paraesthesia of fingers and toes from peripheral neuropathy • Signs of subacute combined degeneration of the spinal cord • Dementia, depression, irritability	• Glossitis, skin hyperpigmentation • Intermittent soreness of tongue • Smooth atrophic tongue • Raw and red tongue during attacks of glossitis • Periodic diarrhoea • Infertility in young females • Possible increased risk of myocardial infarction and stroke (related to elevated homocysteine levels)

Pathogenesis of Neurological Involvement in Vitamin B_{12} Deficiency

- Two mechanisms are responsible for neurologic complications of vitamin B_{12} deficiency:
  - Deficiency of methylcobalamin produces impairment in the conversion of homocysteine to methionine. Methionine is needed for the production of choline and choline-containing phospholipids. These are required by the neuronal cells.
  - Adenosylcobalamin, a B_{12}-containing cofactor, is required for the conversion of methylmalonyl CoA to succinyl CoA. Lack of this cofactor leads to increase in the levels of methylmalonyl CoA and its precursor, propionyl CoA. As a result, non-physiologic fatty acids are synthesised and incorporated into neuronal lipids.
- Severity of megaloblastic anaemia is inversely correlated with degree of neurologic dysfunction.

5-Methyltetra-hydrofolate → Tetrahydrofolate

Methyltransferase

Homocysteine → Methionine

Methylcobalamin

Vitamin B_{12} (Cobalamin)

Adenosylcobalamin

Methylmalonyl-CoA → Succinyl-CoA

Diagnosis

- Macrocytic anaemia.
- Hypersegmented neutrophils in peripheral smear.
- Pancytopenia. Myelodysplastic syndrome (MDS) and aplastic anaemia may also present with macrocytosis, reduced reticulocyte count, and pancytopenia. In MDS, peripheral blood smear and bone marrow shows dysplastic white blood cells while in aplastic anaemia, the marrow shows markedly reduced cellularity.
- Schilling test (see below).
- Low serum vitamin B_{12} levels (<200 pg/μL). May be elevated if patient has associated myeloproliferative disorders, liver disease and intestinal bacterial overgrowth. Levels may be falsely low with folate deficiency, pregnancy and use of oral contraceptives.
- Elevated serum methylmalonic acid (MMA) and homocysteine levels. MMA is also elevated in the presence of renal failure. Homocysteine is also elevated in hereditary homocysteinaemia.
- Low levels of holotranscobalamin II is a useful marker of early vitamin B_{12} deficiency. It can be used in patients with myeloproliferative disorders. Levels may be elevated in renal failure.

Management

- Treatment of underlying cause, whenever possible.
- Vitamin B_{12} therapy (cyanocobalamin, hydroxocobalamin or methylcobalamin may be used).
  - Initial dose of hydroxocobalamin is 1000 μg, deep intramuscularly daily for 1 week.
  - Maintenance dose is 1000 μg of hydroxocobalamin intramuscularly once in a month or 1000 μg of cyanocobalamin once in 3 months indefinitely (only when necessary).
  - An acceptable alternative is to give 1000–2000 μg of vitamin B_{12} orally daily for 1 month followed by 125–500 μg daily indefinitely (only when necessary).
- Iron therapy with ferrous sulphate 200 mg thrice daily orally should be started soon after the commencement of vitamin B_{12} therapy if the patient has associated iron deficiency (dimorphic anaemia—macrocytosis and hypochromia).

Q. Describe briefly Schilling test or vitamin B_{12} absorption test.

- Schilling test demonstrates that there is failure of vitamin B_{12} absorption due to the lack of intrinsic factor. Rarely used at present.

Method and Interpretation

- The fasting patient is given 1 μg of radioactive vitamin B_{12} orally and 1000 μg of vitamin B_{12} intramuscularly. The injected vitamin B_{12} saturates the binding proteins so that the ingested vitamin B_{12} is excreted in urine. Radioactive dose is measured in the 24-hour urine sample.

Stage 1

- Normal persons excrete more than 10% of administered radioactivity in 24-hour urine.
- Patients with intrinsic factor deficiency (e.g., pernicious anaemia) excrete less than 5% of the administered dose.

Stage 2

- The test is then repeated with intrinsic factor added to radioactive vitamin B_{12}. If the defect gets corrected with this, it is assumed that the patient has intrinsic factor deficiency (e.g., pernicious anaemia).

Stage 3

- If the defect is still not corrected, a lesion of the small intestine is likely. Malabsorption due to abnormal bacterial flora in the small intestine may be corrected by a 7-day course of oral tetracycline. The test is repeated after a 7-day course of oral tetracycline. If the defect gets corrected, it is assumed that there is malabsorption of vitamin B_{12} due to abnormal bacterial flora in the small intestine.

Stage 4

- Patient is given pancreatic enzymes for 3 days and the test is repeated. If the defect gets corrected, malabsorption is related to a pancreatic disease.

Q. Give a brief account of folic acid.

Q. Discuss briefly the causes, manifestations, diagnosis and management of folate deficiency.

Folic Acid

- Folic acid (pteroylglutamic acid—PGA) is the parent compound of a group of derivatives, referred to as folates. Folic acid does not exist as such in nature, but is available as a medicinal compound. Body obtains folates from the polyglutamates of food. Absorption is mainly from the jejunum.
- Folate is obtained from both vegetable and animal food stuffs. Much of it is destroyed by cooking.
- Folate is mainly stored in the liver. The stores are exhausted in about 3 months and hence the manifestations of folate deficiency appear in about 3 months.
- Normal daily requirement of folate is 100–200 μg.

Metabolism

Polyglutamates in food

→ Broken in upper intestines

Monoglutamates

Methyl tetrahydrofolate (in blood and tissues)

Homocysteine

Vitamin B$_{12}$ (Methylcobalamin)

Methionine

Tetrahydrofolate

5-formyl tetrahydrofolate (folinic acid)

Dihydrofolate reductase

5,10-methylene tetrahydrofolate

dUMP

Dihydrofolate

dTMP

DNA
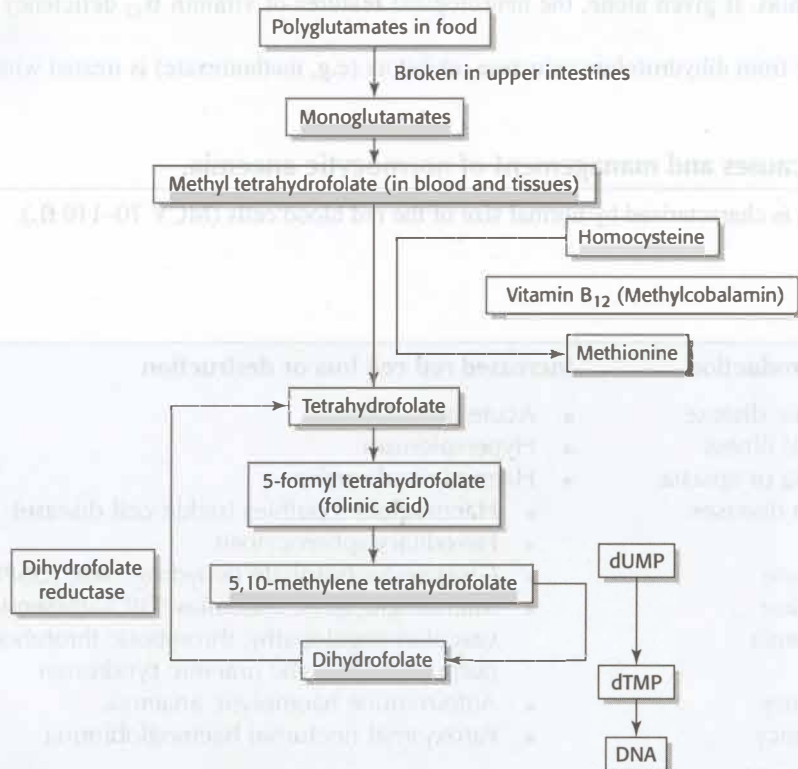
Causes of Folate Deficiency

• Inadequate intake or increased demand	Physiological—pregnancy, lactation, infancy
	Pathological—malignancies, haemolytic anaemias, chronic exfoliative skin disease, chronic inflammatory and infective diseases, haemodialysis
• Malabsorption	Diseases of upper small intestine like tropical sprue, coeliac disease, alcohol, phenytoin, primidone, metformin, cholestyramine
• Antifolate drugs	Methotrexate, trimethoprim, pyrimethamine, pentamidine, 5-fluorouracil, hydroxyurea

Clinical Manifestations

- Features are similar to those seen with vitamin B$_{12}$ deficiency.
- Glossitis.
- Subacute combined degeneration of the spinal cord does not occur.
- Possible increased risk of myocardial infarction and stroke (related to elevated homocysteine levels).

Diagnosis

- Low serum folate levels.
- Low red cell folate level.
- Macrocytic blood picture.
- Megaloblastic bone marrow.
- Normal or slightly reduced serum vitamin B_{12} levels.
- Elevated serum homocysteine level and normal MMA level.

Management

- Folic acid therapy.
  - An initial daily dose of 5 mg orally followed by a maintenance dose of 5 mg orally once a week.
  - All pregnant females should receive folic acid supplements (5 mg/day) by mouth.
  - Folic acid must never be given without vitamin B_{12} in Addisonian pernicious anaemia or other vitamin B_{12} deficiency anaemias. If given alone, the neurological features of vitamin B_{12} deficiency may be aggravated or precipitated.
- Folic acid deficiency from dihydrofolate reductase inhibitors (e.g. methotrexate) is treated with folinic acid (5-formyl tetrahydrofolate).

Q. Enumerate the causes and management of normocytic anaemia.

- Normocytic anaemia is characterised by normal size of the red blood cells (MCV 70–110 fL).

Causes

Decreased red cell production	Increased red cell loss or destruction
- Anaemia of chronic disease	- Acute blood loss
- Anaemia of critical illness	- Hypersplenism
- Marrow hypoplasia or aplasia	- Haemolytic disorders
- Myeloproliferative diseases	- Haemoglobinopathies (sickle cell disease)
- Myelofibrosis	- Hereditary spherocytosis
- Chronic renal failure	- Glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Chronic liver disease	- Microangiopathic anaemias (DIC—disseminated intra-vascularcoagulopathy, thrombotic thrombocytopenic purpura-haemolytic uraemic syndrome)
- Sideroblastic anaemia	
- Hypothyroidism	
- Adrenal insufficiency	- Autoimmune haemolytic anaemia
- Pituitary insufficiency	- Paroxysmal nocturnal haemoglobinuria
Expansion of plasma volume	
- Pregnancy	

Investigations

- Peripheral blood smear (for type of anaemia, anisocytosis of red cells, leucoerythroblastic picture, spherocytes, target cells, basophilic stippling).
- Reticulocyte count—normal, low or high depending upon underlying cause.
- Total leucocyte count and platelet count.
- Other tests depending upon the possible aetiology.

Management

- Treatment is directed towards the underlying disease.

Q. Discuss briefly the anaemia of chronic disease.

- Also known as anaemia of inflammation.
- Most common cause of normocytic anaemia.
- In some patients, MCV may be low in producing microcytic anaemia.
- Pathogenesis multifactorial: interleukin-6, hepcidin (decreases duodenal iron absorption and blocks iron release from macrophages and hepatocytes) and several other pro-inflammatory mediators are involved. Final pathogenetic mechanisms are listed below:
  - Bone marrow suppression.
  - Impaired ability of reticuloendothelial cells to release iron (results in low serum iron).
  - Inadequate production of EPO.
  - Poor response to EPO.
  - Slightly shortened red cell survival.
- It occurs in a wide variety of chronic diseases including inflammatory conditions, neoplasms and various systemic diseases including rheumatoid arthritis, hepatitis, collagen vascular diseases, etc.
- The diagnosis of chronic disease is not usually applied to anaemias associated with renal, hepatic or endocrine disorders.

Investigations

- Peripheral smear showing normocytic normochromic red cells. Some cases show microcytic hypochromic picture.
- Most patients do not have associated leucopenia or thrombocytopenia.
- Reduced serum iron.
- Reduced TIBC.
- Reduced transferrin levels (due to down-regulation of transferrin synthesis as a result of an increase in ferritin).
- Elevated ferritin levels.

Management

- Treat the underlying chronic disease.
- Recombinant human erythropoietin may be tried if the anaemia is not corrected after treatment of the underlying disease.
- Associated iron deficiency may require intravenous iron as elevated levels of hepcidin inhibit GI absorption of iron.

Q. Discuss briefly anaemia of critical illness.

- Anaemia highly prevalent in critically ill and injured patients.
- Approximately 97% become anaemic by day 8 of illness.

Pathogenesis

- A shortened red blood cell circulatory life span.
  - Haemolysis.
  - Losses from phlebotomy and invasive procedure sites.
  - Oozing at injury sites.
  - Gastrointestinal bleeding.
- Diminished red cell production.
  - Nutritional deficiencies.
  - Anaemia of inflammation—impaired proliferation of red cell precursors, impaired iron metabolism, reduced EPO production.

Management

- Blood transfusion:
  - In most critically ill patients, transfuse RBC if Hb <7 g/dL ("restrictive" strategy to maintain it between 7-9 g/dL). However, in patients with acute myocardial infarction or when weaning from ventilator is difficult, blood transfusion may be given to achieve Hb >10 g/dL.
- Minimise blood loss (use of small-volume phlebotomy tubes, point-of-care testing and noninvasive testing, and elimination of unnecessary laboratory studies).
- Erythropoietin is of little benefit.

Q.   What are the causes of pancytopenia?

Pancytopenia with cellular bone marrow	Pancytopenia with hypocellular bone marrow

• Primary bone marrow diseases:
  • Myelodysplastic syndrome (MDS)
  • Myelofibrosis
  • Myelophthisis
  • Hairy cell leukaemia
  • Paroxysmal nocturnal haemoglobinuria
• Systemic diseases:
  • Hypersplenism
  • Folate or vitamin B_{12} deficiency
  • Severe infection
  • Systemic lupus erythematosus
  • Tuberculosis
	• Aplastic anaemia
	• Aleukaemic leukaemia
	• Some MDS

Q.   Define aplastic anaemia. Discuss the aetiology, clinical features, investigations and management of aplastic anaemia.

Definition

- Aplastic anaemia is defined as a condition in which an acellular or markedly hypocellular bone marrow results in pancytopenia (anaemia, granulocytopenia, thrombocytopenia), and there are no leukaemic or abnormal cells in marrow or blood.
- Patients with moderate cytopenia not requiring transfusions are referred to as hypoplastic anaemia.

Classification

• Congenital	Fanconi's anaemia, Diamond–Blackfan anaemia
• Acquired	Primary or idiopathic (no definite cause) Secondary (definite or likely agent can be identified)

Aetiopathogenesis of Aplastic Anaemia (secondary)

• Drug-induced aplasia		
	• Cytotoxic drugs	Alkylating agents, antimetabolites, others
	• Antibacterial drugs	Chloramphenicol, sulphonamides, isoniazid, arsenicals
	• Tranquilisers	Chlorpromazine, meprobamate, chlordiazepoxide, promazine, thioridazine
	• Antirheumatic drugs	Oxyphenbutazone, phenylbutazone, indomethacin, gold salts, diclofenac, D-penicillamine
	• Antidiabetic drugs	Tolbutamide, chlorpropamide
	• Miscellaneous drugs	Chlorthiazide, mepacrine, hydralazine, acetazolamide, potassium perchlorate, carbamazepine, carbimazole
• Chemicals		Benzene, lindane (gamma benzene hexachloride), DDT
• Viral infections		Hepatitis viruses, Epstein–Barr virus, HIV, Parvovirus
• Miscellaneous		Pancreatitis, paroxysmal nocturnal haemoglobinuria, eosinophilic fasciitis, radiation

- Several drugs can produce aplastic anaemia either due to direct toxic effect (dose-dependent, predictable) or idiosyncratic reactions (dose-independent, unpredictable).
- There is strong evidence suggesting that aplastic anaemia is an immune-mediated disease. Genetic factors are also major contributors and it is believed that a predisposing genetics factor with certain environmental factors (damage induced by chemicals, drugs, viruses, or antigens) leads to lymphocyte activation and immune reaction.

Clinical Features

- Clinical features of aplastic anaemia result from the complications of pancytopenia (anaemia, granulocytopenia, thrombocytopenia).
- Anaemia results in weakness, fatiguability, lassitude, dyspnoea on exertion and pallor.
- Granulocytopenia (neutropenia) results in various infections, sore throat, oral and pharyngeal ulcers, fever with chills and sweating, chronic skin infections, recurrent respiratory infections, pneumonia and septicaemia.
- Thrombocytopenia results in various bleeding manifestations, when the platelet count is less than 20,000/μL. These include bleeding into skin (ecchymosis, petechiae), epistaxis, menorrhagia, bleeding from gums and gastrointestinal tract, retinal haemorrhage and cerebral haemorrhage.
- Physical examination characteristically shows that jaundice, splenomegaly and lymphadenopathy are absent. The presence of these should prompt one to search for an associated disease or alternate diagnosis.
- Aplastic anaemia may coexist or evolve to clonal disorders, like paroxysmal nocturnal haemoglobinuria (PNH), myelo-dysplastic syndrome (MDS) or acute myeloid leukaemia.

Fanconi's Anaemia

- Autosomal recessive.
- Congenital malformations—short stature, microphthalmia, cataracts, absence or hypoplasia of radius, micrognathia, ectopic kidney, horse-shoe kidney, patent ductus arteriosus, ventricular septal defect, pulmonic stenosis, coarctation of aorta, oesophageal or duodenal atresia, intestinal malrotation, microcephaly, hydrocephalus, micropenis, undescended testes, hypoplasia of uterus and vagina, prominent ears, deafness.
- Progressive pancytopenia.
- Predisposition to both haematologic malignancies (MDS, acute myeloid leukaemia) and solid tumours (squamous cell carcinomas of head and neck and anogenital region).

Diagnosis

- Haemoglobin is reduced.
- Corrected reticulocyte count is low.
- Leucopenia and thrombocytopenia.
- Peripheral smear study:
  - Normocytic, normochromic anaemia.
  - Neutropenia with relative lymphocytosis.
- Bone marrow study:
  - Markedly hypocellular or acellular marrow with no malignant infiltrates or fibrosis.
  - Haemopoietic cells are markedly reduced to absent.
  - Increase in fat cells.
  - Bone marrow iron stores are usually increased.
  - Serum iron and transferrin saturation are increased.
  - Ferrokinetic studies show delayed clearance of radioactive iron from the blood and increased uptake by the liver.

Severe Aplasia

- A marrow biopsy showing less than 25% of normal cellularity
  OR
- Marrow biopsy showing less than 50% normal cellularity in which fewer than 30% of the cells are hematopoietic and at least two of the following criteria:
  - Granulocyte count less than 500/μL (If granulocyte count < 200/ μL, it is known as very severe aplastic anaemia)
  - Platelet count less than 20,000/μL
  - Anaemia with corrected reticulocyte count less than 1%

Management

- Removal of the causative agent wherever possible (see aetiology).
- Supportive therapy includes prevention and treatment of infections and haemorrhage, and red cell transfusion for anaemia. Prophylactic platelet transfusions are given if platelet count is <10,000/ μL.

- In severe aplastic anaemia, haematopoietic stem cell transplantation should be considered in patients under the age of 40, who have HLA-identical donors. Patients above the age of 40 have a high risk of graft-versus-host disease.
- Medical measures to stimulate haemopoiesis and promote marrow recovery are indicated in patients above 40 years of age or when HLA-identical donor is not available.
  - Combination of anti-thymocyte globulin (ATG) or anti-lymphocyte globulin (ALG) along with cyclosporine is the standard medical treatment with 60-70% response rate..
  - Cyclosporine alone if the patient cannot afford ATG. The dose is 3–7 mg/kg/day in two divided doses for at least one year before tapering.
  - Alemtuzumab, a monoclonal antibody against CD52 antigen which is found on the surface of many T-lymphocytes can be used to treat aplastic anaemia refractory to above treatment.
  - Androgens (e.g. oxymethalone) are sometimes useful in moderate cases.
  - Steroids have little role in aplastic anaemia but are useful in reducing side effects of ATG/ALG. However, steroids may be useful in children with congenital pure red cell aplasia (Diamond–Blackfan syndrome) and in some adults with pure red cell aplasia.
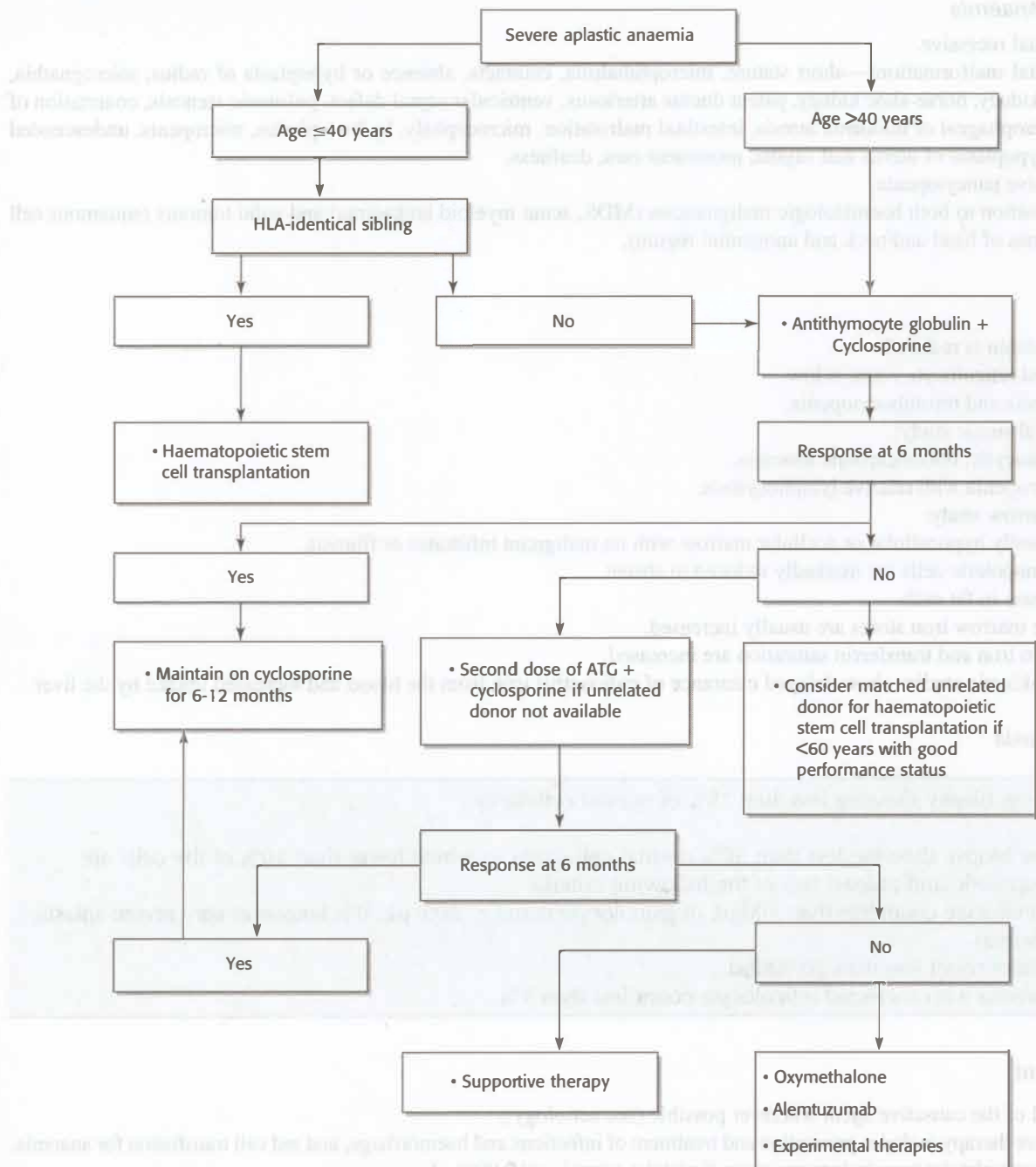
Q. Discuss the aetiology, classification, clinical features, diagnosis and management of haemolytic anaemias.

- Haemolytic anaemias result from an increased rate of red cell destruction. The life span of red cells (normal 90–120 days) is shortened.
- Marrow can compensate for increased red cell destruction by increased production of red cells (up to eight folds).

Classification and Causes

Due to intraerythrocytic defects
- Congenital — Membrane defects—hereditary spherocytosis, hereditary elliptocytosis
  Haemoglobin defects—sickle-cell anaemia, thalassaemias, other abnormal haemoglobins (HbC, HbD, etc.)
  Enzyme defects—G6PD deficiency, pyruvate kinase deficiency
- Acquired — Paroxysmal nocturnal haemoglobinuria

Due to extraerythrocytic defects
- Antibodies (autoimmune and alloimmune)
- Mechanical (e.g. prosthetic heart valves, microangiopathic haemolytic anaemia)
- Drugs (e.g. dapsone, primaquine)
- Infections (e.g. malaria)
- Inflammatory and neoplastic diseases

Clinical Features of Haemolysis

- Clinical features common to haemolysis are listed below. Symptoms and signs specific for individual diseases are considered under respective diseases.

History
- Mild jaundice.
- Symptoms of anaemia.
- Urine is normal in colour on passing (acholuric), but turns dark on standing due to oxidation of urobilinogen to urobilin.
- Black urine ("black water") with haemoglobinuria in case of intravascular haemolysis (malaria, mismatched blood transfusion, G6PD deficiency).
- Symptoms of cholelithiasis may be present. Chronic haemolysis is associated with an increased incidence of pigmented gall stones.
- Acute crisis in many chronic haemolytic anaemias that produces sudden fall in haemoglobin and sometimes, fever, joint pains and abdominal pain.
- Splenic pain from rapid enlargement of spleen or splenic infarction.
- Infections.
- Family history is important in congenital haemolytic anaemias.

Physical Findings
- Mild jaundice.
- Anaemia.
- Splenomegaly in some cases.
- Chronic leg ulcers in some cases.
- In some congenital haemolytic anaemias, skeletal hypertrophy occurs due to increased erythropoiesis causing expansion of bone marrow. This manifests as enlargement of maxillary bones and frontal bossing and malocclusion of the teeth due to overgrowth of upper jaw.
- Signs of systemic diseases predisposing to haemolysis.
- Signs of cholelithiasis (cholecystitis or obstruction).

Diagnosis

- Diagnosis of haemolytic anaemias can be considered under two headings, recognition of haemolysis and recognition of cause of haemolysis.

Recognition of Haemolysis

- Evidences of increased erythrocyte destruction.
  - Unconjugated hyperbilirubinaemia, usually less than 6 mg/dL. May not be present in all cases as it depends on the capacity of liver to conjugate and excrete bilirubin.
  - Increased urobilinogen excretion in urine.
  - Decreased plasma haptoglobin and haemopexin.
  - Increased plasma LDH.
  - Demonstration of shortened red cell lifespan (^{51}Cr-labelled red blood cells).
- Evidences of increased erythrocyte production.
  - Increased reticulocyte count (reticulocytosis).
  - Macrocytosis (due to increased reticulocyte count and folate deficiency), polychromasia, and nucleated red cells in peripheral smear.
  - Spherocytes in hereditary spherocytosis and autoimmune haemolytic anaemia.
  - Marked anisopoikilocytosis, hypochromic red cells and target cells seen in thalassaemias.
  - Fragmented red cells in microangiopathic anaemias and prosthetic cardiac valve.
  - Erythroid hyperplasia of bone marrow.
  - Radiological changes in congenital haemolytic anaemias, e.g. "hair on end" appearance in skull radiograph.
- Evidences specific to intravascular haemolysis.
  - Haemoglobinaemia.
  - Haemoglobinuria.
  - Methaemoglobinaemia (in some cases).
  - Haemosiderinuria (haemosiderin in urine) as demonstrated by Prussian blue staining. Seen in chronic intravascular haemolysis.

Recognition of Cause of Haemolysis

- Details regarding the identification of cause of haemolysis is dealt with in detail under individual diseases.
- However, the commonly done tests include one or more of the following:
  - Peripheral smear examination (sickle cells, spherocytes, red cell fragments).
  - Coombs' test.
  - Haemoglobin electrophoresis.
  - Heinz body preparation.
  - Osmotic fragility, sucrose lysis and Ham's test.
  - Measurement of enzyme activity.

Treatment

- Supportive therapy:
  - Blood transfusions.
  - Treatment of infections.
  - Treatment of leg ulcers.
  - Treatment of symptomatic cholelithiasis.
  - Splenectomy in selected cases.
- Specific therapies for individual diseases are dealt with under respective diseases.

Q. Briefly outline hereditary spherocytosis.

- Autosomal dominant inheritance in more than 75% cases.
- Characterised by deficiency of ankyrin, spectrin, band-3 or protein 4.2—transmembrane proteins that link the bilayer of red cells to the membrane skeleton.
- This results in spherical erythrocytes (spherocytes) that are more susceptible to osmotic lysis. However, the primary cause of anaemia is that the red cells with decreased membrane surface area are unable to effectively traverse the spleen; they are sequestered and removed from circulation by the spleen.

Clinical Features

- Strong family history of anaemia, jaundice, splenomegaly and cholelithiasis.
- 25% of the patients have mild compensated haemolysis, minimal spherocytosis, near normal haemoglobin levels, slight reticulocytosis (<6%) and mild splenomegaly.
- In children, there is growth retardation due to haemolysis and bone changes due to marrow hypertrophy.
- In adults, there is anaemia, intermittent jaundice and moderate splenomegaly.
- Regular blood transfusions are required in a small number of patients who have severe disease that is transmitted through autosomal recessive mechanism.

Complications

- Chronic leg ulcers.
- Cholelithiasis.
- Haemolytic crises (probably due to enlargement of spleen during infections and activation of reticuloendothelial system).
- Aplastic crises due to parvovirus B19 infection which selectively infects erythropoietic progenitor cells and inhibits their growth.

Investigations

- Demonstration of a haemolytic state (see above).
- Demonstration of spherocytes in the blood film.
- The mean corpuscular volume (MCV) is normal or slightly decreased in most patients, except in severe cases, when it is decreased. The mean corpuscular haemoglobin concentration (MCHC) is increased (≥34.5 g/dL) due to relative cellular dehydration in more than 50% of patients.
- Increased osmotic fragility (may be absent in mild cases; may be positive in autoimmune haemolytic anaemia).
- Reduced florescence of eosin-5-maleimide-labeled erythrocytes in flow cytometry-base analysis.
- Negative Coombs' test.
- Demonstration of same disorder in other family members.

Treatment

- Splenectomy is the treatment of choice. It should not be done until the age of 6 years. Splenectomy should be preceded by pneumococcal and *Haemophilus influenzae* immunisation, and followed by penicillin prophylaxis (Pen-V 500 mg BID) in young children. Patients with mild features and well-compensated haemolysis can be managed expectantly, deferring splenectomy unless clinically indicated.
- Folic acid supplementation in un-splenectomised patients.

Q. Discuss the aetiology, precipitating causes, clinical features, investigations and management of glucose-6-phosphate dehydrogenase (G6PD) deficiency.

- Glucose-6-phosphate dehydrogenase (G6PD) is the first enzyme in the hexose monophosphate shunt of the Embden–Meyerhof pathway, providing reducing power to all cells in the form of NADPH (reduced form of nicotinamide adenine dinucleotide phosphate). Since red blood cells do not contain mitochondria, this pathway is their only source of NADPH; therefore, defence against oxidative damage is dependent on G6PD.
- G6PD deficiency is an X-linked disorder resulting in G6PD variants with different levels of enzyme activity. It is the most common enzyme deficiency.
- Red cells deficient in G6PD are unable to keep glutathione in reduced state. This results in impaired response to oxidising drugs or toxic injury.
- Over 250 variants of G6PD have been described suggesting genetic heterogeneity. The three common variants are:
  - G6PD (A-) seen in African blacks; degree of deficiency is mild and haemolysis is self-limiting.
  - G6PD (B-) or G6PD Mediterranean, seen in the Mediterranean area. It is the severe form of deficiency. This is the most common variant seen in India (other variants reported from India include G6PD Kerala–Kalyan, and G6PD Orissa).
  - G6PD Canton seen in Chinese.

Precipitating/Aggravating Causes of Haemolysis

- Drugs (haemolysis is dose-related)---e.g. primaquine, quinine, dapsone, chloroquine, aspirin, ascorbic acid, sulphonamides (particularly sulphanilamide, sulphacetamide, sulphapyridine, sulphamethoxazole), nitrofurantoin, L-dopa, dapsone, quinidine, nalidixic acid, vitamin K, phenacetin, phenazopyridine, cotrimoxazole, methylene blue, nitrofurantoin.
- Toxins—naphthalene.
- Viral and bacterial infections (e.g. hepatits A and B, Salmonella).
- Diabetic acidosis, myocardial infarction, strenuous exercise.
- Broad bean—*Vicia faba* (in Mediterranean variety).

Clinical Features

- Most patients are asymptomatic unless any of the incriminated drugs or foods are ingested. The exposure is followed by haemolysis, rapid development of anaemia and haemoglobinuria (cola coloured urine). Rarely anuria occurs.
- Favism is haemolysis following ingestion of the broad bean, *Vicia faba*. It is a feature of the Mediterranean type.
- Neonatal jaundice is a feature of Mediterranean type. Haemolysis does not seem to contribute to it as much as impaired bilirubin conjugation and clearance by the liver. Severe neonatal jaundice if untreated could give rise to kernicterus.
- Chronic non-spherocytic haemolytic anaemia. Many such patients have a history of severe neonatal jaundice, chronic anaemia exacerbated by oxidative stress that typically requires blood transfusions, reticulocytosis, gallstones and splenomegaly. Haemolysis is mainly extravascular.
- In the African variety, growth of *P. falciparum* in red cells is markedly slow, and hence, these patients are protected from malaria.

Investigations

- Evidences of intravascular haemolysis.
- Anaemia that worsens until days 7–8.
- Heinz bodies (denatured haemoglobin precipitates) in peripheral red blood cells.
- Diagnosis is confirmed by estimating G6PD activity of the red cell. This should be done several days after the acute episode. Estimation of G6PD activity during or immediately after acute haemolysis may give a false normal value as the young red cells and reticulocytes have near-normal G6PD levels.

Management

- Removal of the offending agent and avoiding its further use.
- Supportive therapy for anaemia like blood transfusion.
- Treatment of infection.

Q. Describe the structure of normal haemoglobin.

- Haemoglobin is a conjugated protein of molecular weight 64,000. It consists of two pairs of polypeptide chains to each of which a haem is attached. Each polypeptide chain is composed of a number of amino acids. Iron is in the form of ferrous state (Fe^{++}). Abnormalities resulting in conversion into ferric state lead to abnormal haemoglobin that is not capable of binding oxygen.
- Based on the number and sequence of amino acids, polypeptide chains are classified into the following types:

• Alpha chains (α)	• Gamma chains (γ)	• Epsilon chains (ϵ)
• Beta chains (β)	• Delta chains (δ)	• Zeta chains (ζ)

- There are 3 embryonic haemoglobins seen in the early embryonic period: Hb Portland I ($\zeta_2 \gamma_2$), Hb Gower I ($\zeta_2 \epsilon_2$), Hb Gower II ($\alpha_2 \epsilon_2$). Later in foetal life, there is a switch to the production of α and γ chains, resulting in Hb-F. At birth, there is an additional switch from the production of γ chains to the production of β and δ chains, resulting in Hb-A and Hb-A2.

- Haemoglobin A (Hb-A) that comprises about 97% of the haemoglobin of adult red cells, consists of two alpha and two beta chains ($\alpha_2\beta_2$).
- Haemoglobin F (Hb-F) that accounts for about 70–90% of foetal haemoglobin consists of two alpha and two gamma chains ($\alpha_2\gamma_2$).
- The normal haemoglobins seen in the adult are Hb-A and Hb-A_2 ($\alpha_2\delta_2$) and the foetus are Hb-F and Hb-Bart's (γ_4).

Q. How do you classify haemoglobinopathies (hereditary disorders of haemoglobin; disorders of haemoglobin structure and synthesis)?

- Haemoglobinopathies are disorders that are due to structural abnormalities in the globin chains of haemoglobin (qualitative defect). However, in practice, this term applies to disorders that affect the structure, function or production of haemoglobin due to abnormalities in the formation of globin.

Classification

Qualitative haemoglobinopathies	Quantitative haemoglobinopathies
- Haemoglobin S	- Thalassaemias (α, β-thalassaemia)
- Haemoglobin C	**Combined qualitative and quantitative haemoglobinopathies**
- Haemoglobin D Punjab	- Haemoglobin E
- Altered oxygen affinity	- Sickle-cell β-thalassaemia
- High affinity haemoglobin	
- Low affinity haemoglobin	**Acquired haemoglobinopathies**
- Haemoglobins that oxidise easily	- Methaemoglobinaemia
- Unstable haemoglobin	- Carboxyhaemoglobinaemia
- M haemoglobin	

- Qualitative abnormality of haemoglobin results from alterations in the amino acid sequence of the polypeptide chains that produce structurally defective haemoglobins.
- Quantitative abnormality of haemoglobin results from impaired or absent polypeptide chain formation but amino acid sequence is normal.

Inheritance

- Subjects who inherit one normal and one abnormal gene are heterozygotes. The heterozygous state is usually referred to as the trait (e.g. sickle-cell trait; Hb-S trait; Hb-AS).
- Subjects who inherit two identical abnormal genes are homozygotes. The homozygous state is usually referred to as the disease (e.g. sickle-cell disease or Hb-S disease or Hb-SS).
- Subjects who inherit two different abnormal genes are double heterozygotes (e.g. Hb-SC; Hb-S β-thalassaemia, etc.).

Q. Discuss the pathogenesis, clinical features, investigations and management of sickle-cell anaemia.

- Sickle-cell anaemia results from an abnormal haemoglobin known as haemoglobin-S (Hb-S) or sickle-cell haemoglobin. The molecular lesion in Hb-S is the substitution of valine for glutamic acid at the sixth residue of the beta chain (Hb-S6$^{GLU-VAL}$).
- Sickle-cell anaemia is the homozygous state for the Hb-S gene (*Hb-SS*). It is transmitted as an autosomal recessive disease.
- The heterozygous state (Hb-AS) is known as sickle cell trait.
- In India, it is common among certain tribes in South India, Assam, Bihar and Orissa.

Pathogenesis

- Deoxygenation causes the red cells containing Hb-S to become rigid and deformed, assuming a sickle or crescent shape (sickle-shaped cells). These changes are reversible with reoxygenation. However, the sickling may become permanent, and then the red cells are called irreversibly sickled.
- The consequences of sickling are the following:
  - Occlusion of microvascular circulation by the sickle cells leading to tissue ischaemia and infarction (infarction crisis). Vaso-occlusion also involves leucocytes, activated endothelial cells, altered nitric oxide metabolism and hypercoagulability.
  - Destruction of the sickle cells by the reticuloendothelial system resulting in haemolysis.

Factors Promoting Sickling

- Haemoglobin F (Hb-F) strongly inhibits sickling. Sickle cell disease in India is associated with elevated Hb-F and hence is a mild disorder.
- Hb-S confers some protection against *Plasmodium falciparum* malaria, so that these patients are relatively resistant to malaria.

• Fever	• Hb-C and Hb-D
• Sluggish blood flow	• Increase in red cell 2,3-DPG
• Low oxygen tension	• Reduction in red cell water content
• Low pH (acidosis)	

Clinical Features in Children

- Clinical manifestations are absent in the first 6 months of life, since high Hb-F levels protect the red cells from sickling.
- Infections with pneumococcus, meningococcus, *E. coli* and *H. influenzae* are common. Pneumococcal meningitis or pneumonia with septicaemia is particularly common.
- Hand–foot syndrome (dactylitis) is due to micro-infarction of carpal and tarsal bones.
- Splenic sequestration syndrome is sudden pooling of blood within the spleen resulting in splenomegaly, hypovolaemia and shock, requiring prompt blood transfusions.
- Splenomegaly is present throughout early childhood. But repeated episodes of splenic infarction ultimately lead to atrophy of the spleen (autosplenectomy). By about 8 years of age, spleen is no longer palpable and is reduced to a small fibrous remnant.
- Acute chest syndrome occurs in both children and adults. It indicates occurrence of a new pulmonary infiltrate on chest radiograph and can develop because of infection, fat embolism or vaso-occlusion of pulmonary vasculature. It is usually accompanied by pain in the chest, fever, respiratory distress and hypoxaemia.
- Others are acute coronary syndrome and stroke.

Clinical Features in Adults

Anaemia

- Severe haemolytic type of anaemia.
- Secondary folate deficiency exacerbates anaemia.
- Chronic anaemia results in fatigue, frequent infections, cardiomegaly and systolic murmur.

Infarction Crises (Vaso-occlusive crisis)

- The most common manifestations are sudden attacks of bone pain and abdominal pain with or without fever.
- Bone pain is due to ischaemia and infarction. Avascular necrosis of the head of femur is common.
- Mesenteric infarction results in acute abdominal pain.
- Splenic infarction and autosplenectomy (refer back).
- Cerebral infarction results in hemiplegia.
- Pulmonary infarction results in acute chest syndrome. This manifests as acute chest pain and pulmonary infiltrates on chest radiograph mimicking pneumonia. Typically, the acute chest syndrome presents three days after the start of a vaso-occlusive crisis.

- Infarction of renal papillae results in haematuria.
- Retinal microinfarcts result in loss of vision.

Aplastic Crises

- Aplastic crisis results from temporary marrow suppression following infections, particularly with human parvovirus B19.

Haemolytic Crises

- Haemolytic crises are episodes of increased sequestration and destruction of red cells. It clinically manifests as an abrupt fall in haemoglobin and rapid enlargement of liver and spleen.

Other Manifestations

- Stroke, acute coronary syndrome, cardiac arrhythmias.
- Chronic leg ulcers.
- Cholelithiasis.
- *Salmonella* osteomyelitis.
- Proteinuria, pyelonephritis, renal papillary necrosis, renal failure.
- Priapism.
- Pulmonary hypertension.
- Frontal bossing of the skull, prominent malar bones and protuberant teeth resulting from marrow hyperplasia.
- Iron overload due to repeated transfusions.

Investigations

- Demonstration of a haemolytic state.
- Peripheral blood can show features of hyposplenism (Howell–Jolly bodies, target cells and irregularly contracted red cells).
- "Sickle test" is demonstration of sickling of the red cells when mixed with a solution of sodium metabisulphite.
- Haemoglobin solubility tests.
- Haemoglobin electrophoresis. There is no Hb-A, 80–95% Hb-SS and 2–20% Hb-F. In sickle cell trait (heterozygous state), Hb-S is 20–40% and the rest is Hb-A.
- Tests for iron overload (serum ferritin levels, transferrin saturation, liver iron concentration using liver biopsy specimen, measurement of liver iron using MRI).
- Antenatal diagnosis is by analysing DNA from the amniotic fluid cells at 7–10 weeks of gestation.

Management

- General measures:
  - Folic acid supplementation, 5 mg daily.
  - Avoidance of chilling, dehydration and hypoxia.
  - Prevention and prompt identification and treatment of infections with antibiotics.
  - Phenoxymethyl penicillin 250 mg daily starting at the age of 2 months and continued for 5 years.
  - Pneumococcal vaccination in young patients. Also in adults who have hyposplenism.
- Blood transfusion:
  - Transfusion required to increase oxygen carrying capacity, replace rigid, sickle-shaped red cells with normal, deformable cells, thereby reducing haemolysis and restoring blood flow. It also reduces HB-S production.
  - Indicated for severe anaemia due to aplastic crisis and acute splenic sequestration.
  - Exchange transfusion to reduce Hb-S to below 30% with increase in haemoglobin to more than 10 g/dL is recommended for severe acute chest syndrome, severe sepsis and acute stroke.
  - Chronic transfusion to keep Hb-S below 30% is mainstay of secondary prevention of overt stroke.
- Infarction crises are managed with hydration, oxygen, analgesics and transfusion with red cell concentrate in selected cases.
- Splenic sequestration crisis is treated with blood transfusions.
- Recurrent strokes (cerebral infarcts) are treated with chronic monthly exchange transfusions.
- Acute chest syndrome is treated with antibiotics, maintenance of arterial oxygenation and if required, exchange transfusion.

- Aplastic crisis is treated with red cell transfusions to maintain haemoglobin.
- Chronic leg ulcers are managed with elevation of limb, daily dressings with zinc sulphate and exchange transfusion in extreme cases.
- Hydroxyurea (hydroxycarbamide) may be used in patients with severe symptoms. It increases the production of Hb-F and reduces vaso-occlusive crisis.
- Management of iron overload using iron chelators (deferoxamine, deferiprone or deferasirox).
- Haemopoietic stem cell transplantation is curative.

Q. Give a brief account of methaemoglobinaemia.

- Normal oxygen transport depends on the maintenance of haemoglobin in the reduced (Fe^{++}) state. When haemoglobin is oxidised to methaemoglobin, the haem iron becomes Fe^{+++} and is incapable of binding oxygen. Normal red cells contain less than 1% methaemoglobin. An excess of methaemoglobin in the blood is termed methaemoglobinaemia. Clinically, when methaemoglobin level exceeds 1.5 g/dL, the patient develops cyanosis. At higher levels, they develop headache, weakness and breathlessness (due to hypoxia).

Causes

- Methaemoglobin reductase deficiency (congenital).
- Acquired methaemoglobinaemia resulting from exposure to certain drugs and toxins, e.g. nitrites and nitrates, primaquine, dapsone, phenacetin, phenazopyridine, metoclopramide, nitroglycerine.
- M haemoglobins (haemoglobin variants). Five haemoglobin variants are identified—Hb M Boston, Hb M Iwate, Hb M Saskatoon, Hb M Hyde Park and Hb M Milwaukee.

Treatment

- Methaemoglobin reductase deficiency is treated with oral methylene blue or ascorbic acid.
- Severe methaemoglobinaemia is treated with intravenous methylene blue.
- M haemoglobins require no treatment.

Q. What are thalassaemias? What are the common forms and genetics of thalassaemias?

- The fundamental defect in thalassaemias is a reduction or absence of synthesis of one of the globin chains.
- There are two main groups of thalassaemias:
    - α-thalassaemia, where the synthesis of α chains is affected.
    - β-thalassaemia, where the synthesis of β chains is affected.

Common Forms

α-thalassaemias	β-thalassaemias
• α-thalassaemia trait	• β-thalassaemia minor (heterozygous state)
• Haemoglobin-H disease	• β-thalassaemia intermedia
• Haemoglobin-Bart's (hydrops foetalis)	• β-thalassaemia major (Cooley's anaemia; homozygous state)

Genetics

- In homozygous β-thalassaemia, either no normal β-chains are produced (β°) or β-chain production is markedly reduced (β⁺). The excess α-chains combine with whatever β, γ and δ chains are produced, resulting in increased quantities of Hb A_2 and Hb F, and at best, a small amount of Hb A. Thalassaemia intermedia, may be due to β⁺/β⁺, β°/β⁺ or a combination of β⁺ and α-thalassaemia, where there is reduced α-chain precipitation and less ineffective erythropoiesis and haemolysis. It may also be due to combination of hereditary persistence of Hb-F with homozygous β-thalassaemia.
- There are four genes for α-chain, two on each chromosome. Deletion of one α-chain gene (α⁺) or both α-chain genes (α°) on each chromosome may occur. Deletion of one α-gene from one or both chromosomes produces α-thalassaemia trait. Deletion of three α-genes produces Hb H ($β_4$). If all four genes are absent, there is no α-chain synthesis and only

Hb Bart's (γ_4) is present. It is incompatible with life. The infants are either stillborn at 28–40 weeks or die very shortly after birth. They are pale, oedematous, and have large liver and spleen (hydrops foetalis).

Q. Discuss the clinical features, salient investigations and management of β-thalassaemia major (Cooley's anaemia).

- β-thalassaemia major is the homozygous state of β-thalassaemia. β chain synthesis is absent or grossly reduced.
- In India, common among communities like Sindhi, Punjabi, Gujarat, Parsee. Less common in South India.
- Anaemia occurs due to combined RBC destruction in the bone marrow (ineffective erythropoiesis) and spleen.
- Anaemia and poor tissue oxygenation stimulate increased kidney EPO production that further drives marrow erythropoiesis, resulting in increased ineffective marrow activity and the classic bony deformities.

Clinical Features

- Severe anaemia (usually develops at 6–24 months of age) and its complications.
- Growth and development retardation, feeding problems, diarrhoea and irritability.
- Splenomegaly, at times massive.
- Hepatomegaly.
- Bone marrow hyperplasia resulting in deformities of long bones of legs and craniofacial changes (bossing of the skull, prominent malar eminence, depression of bridge of nose, tendency to a mongoloid slant of the eye and hypertrophy of the maxillae, which tends to expose the upper teeth).
- Development of masses from extramedullary haematopoiesis. Paraspinal masses may produce cord compression.
- Increased risk of thrombosis particularly in patients who are non-transfused or infrequently transfused and in patients who are splenectomised.
- Deposition of iron in tissues (haemosiderosis) resulting in organ failure. This may be due to increased gastrointestinal absorption of iron and can occur even without exogenously administered iron.
  - Pancreatic haemosiderosis resulting in diabetes.
  - Hepatic haemosiderosis resulting in cirrhosis.
  - Cardiac haemosiderosis resulting in arrhythmias, heart blocks and congestive heart failure (primary causes of death).
  - Deposition of iron in various endocrine organs leads to growth hormone deficiency, delayed puberty, hypogonadotropic hypogonadism, impaired glucose metabolism and type 1 diabetes mellitus, osteopaenia, hypothyroidism, and hypoparathyroidism.
- Appropriately treated patients can survive beyond 40 years of age.

Investigations

- Severe microcytic, hypochromic anaemia with poikilocytosis (spiculated tear drop and elongated cells), target cells and nucleated red cells.
- Osmotic fragility test shows increased resistance to haemolysis.
- Markedly reduced or absent levels of haemoglobin A (Hb-A).
- Raised levels of haemoglobin F (>92%).
- Skull radiograph shows a "hair on end" appearance and generalised widening of medullary spaces.
- Evidence that both parents have thalassaemia minor.

Management

- Folic acid supplementation.
- Repeated blood transfusions to maintain Hb >10 gm/dL. Regular transfusions suppress erythropoiesis to provide prevention of skeletal deformities and splenomegaly, and inhibit increased gastrointestinal iron absorption.
- Desferrioxamine therapy to chelate iron and enhance iron excretion. Indicated if serum ferritin >1500 µg/L. Deferiprone and deferasirox are oral iron chelators.
- Splenectomy is indicated in children with massive symptomatic splenomegaly, and those with progressively increasing transfusion requirements (above 200–250 mL/kg/year of packed red blood cells).
- Allogenic bone marrow transplantation in young patients.
- Management of associated complications like congestive heart failure and endocrinopathies.

Q. Discuss briefly thalassaemia minor (trait) and thalassaemia intermedia.

Thalassaemia Minor

- Also called β-thalassaemia carrier or β-thalassaemia trait.
- This common carrier state is usually asymptomatic.
- Anaemia is mild or absent.
- Peripheral blood smear shows severely microcytic and hypochromic red cells with target cells.
- The red cell distribution (RDW) may assist in differentiating iron deficiency and sideroblastic anaemia from thalassaemia. RDW will be elevated in >90% of persons with iron deficiency, but in only 50% of persons with thalassaemia. RDW is usually elevated in sideroblastic anaemia.
- Serum iron and ferritin are normal.
- Haemoglobin electrophoresis shows a raised Hb-A_2 (3.5–7.5%) and often a raised Hb-F (0.5–4.0%).
- Avoid iron unless iron deficiency has been documented.
- Genetic counseling is important to prevent transmission of carrier state from both parents.
- Prenatal diagnosis in high-risk pregnancy by chorionic villi biopsy at 11 weeks.

Thalassaemia Intermedia

- Patients generally have mild to moderate anaemia (Hb 7–9 gm/dL).
- Patients may have mild splenomegaly, bone deformities, gall stones and chronic leg ulcers.
- Blood transfusions are usually not required.
- Folic acid supplementation should be provided.

Q. Give a brief account of paroxysmal nocturnal haemoglobinuria (PNH).

- An acquired non-malignant clonal expansion of one or more haematopoietic stem cells.
- The stem cells and their progeny have deficient CD55 and CD59 proteins on their membrane (acquired membrane defect). This makes the red cells susceptible to complement-mediated, intravascular lysis through alternate pathway.

Clinical Features

- Mainly seen in adults, usually in middle age. Both sexes equally affected.
- Presents with passage of dark coloured urine, typically at night or in the morning; occurs intermittently.
- Dysphagia due to oesophageal spasm and abdominal pain in 10% cases.
- Mild jaundice and mild hepatosplenomegaly often present.
- Intravascular thrombosis frequent; may develop in cerebral, portal or mesenteric vessels.
- May begin as or progress to aplastic anaemia.

Diagnosis

- Investigations show anaemia, reticulocytosis, varying degrees of thrombocytopenia and leucopenia, raised bilirubin, and haemosiderinuria.
- Cellular bone marrow with erythroid hyperplasia.
- Diagnosis is confirmed by Ham's test and sucrose lysis test.
  - Ham test checks whether red blood cells become more fragile when they are placed in mild acid.
  - In sucrose lysis test, patient's red cells are placed in low-ionic-strength solution of sucrose and observed for haemolysis.
  - These tests cannot reliably detect small populations of the affected red cells.
  - Ham test can also be positive in congenital dyserythropoietic anaemia and the sucrose lysis test can be positive in megaloblastic anaemia and autoimmune haemolytic anaemia.
- Deficiency of CD57 and CD59 as shown by flow cytometric method is a rapid and sensitive test for diagnosis.

Treatment

- Mainly supportive with blood transfusions and control of infections.
- Iron therapy often required due to loss in urine.

- Steroids may be useful in some cases.
- Eculizumab:
  - Inhibits complement-mediated intravascular haemolysis by blocking formation of membrane attack complex (MAC—consists of C5b, C6, C7, C8 and C9), the cytolytic component of complement system.
  - Eculizumab is a humanised monoclonal antibody that binds to complement C5, preventing its activation to C5b and thereby inhibiting MAC formation.
- Stem cell transplantation is curative.

Q. Give a brief account of autoimmune haemolytic anaemias.

Q. What is the significance of Coombs' test?

Q. Discuss cold haemagglutinin disease (CHAD) in brief.

Q. Write briefly on paroxysmal cold haemoglobinuria (PCH).

Q. Write short note on drug-induced immune haemolytic anaemia.

Autoimmune Haemolytic Anaemias (AIHA)

- A group of acquired disorders in which antibodies develop against red cell antigens. These antibodies cause destruction of red cells resulting in haemolytic anaemia.
- Autoimmune haemolytic anaemias may be classified in two ways:
  1. Based on the type of antibody.
  2. Based on aetiology.

Classification

Based on antibody type	Based on aetiology
• Warm antibody autoimmune haemolytic anaemia (warm AIHA)	• Idiopathic autoimmune acquired haemolytic anaemia (50%)
• Drugs (e.g. methyldopa, penicillins, quinidine)	• Secondary autoimmune acquired haemolytic anaemia (50%)
• Autoimmune disorders (SLE, others)	• Drugs—e.g. methyldopa, penicillins, quinidine
• Idiopathic	• Chronic lymphocytic leukaemia (CLL)
• Chronic lymphatic leukaemia	• Lymphomas
• Hodgkin's lymphoma	• *M. pneumoniae* infection
• Cold antibody autoimmune haemolytic anaemia (cold AIHA)	• Infectious mononucleosis
• Cold haemagglutinin disease (CHAD)	• SLE and other connective tissue
• Paroxysmal cold haemoglobinuria (PCH)	
• Associated with mycoplasma, lymphoma	
• Associated with IgM-monoclonal gammopathy of undetermined significance	

- Warm antibody autoimmune haemolytic anaemia (warm AIHA) is caused by antibodies that react with red cells at 37°C. Majority of them are of the IgG class. Red cells are coated with IgG or IgG plus C3d.
- Cold antibody autoimmune haemolytic anaemia (cold AIHA) is caused by antibodies that react with red cells at below 20°C, and majority of them are of the IgM class. Red cells are usually coated with C3d only.

Warm Antibody Autoimmune Haemolytic Anaemia

- Rhesus (Rh) polypeptides are the commonest targets for the autoantibodies in patients with warm AIHA.
- Most patients with idiopathic warm AIHA are women in their fourth or fifth decade of life.

- Clinical features include anaemia, jaundice, hepatosplenomegaly (, 20% cases) and manifestations of underlying disease. Acute cases present with intravascular haemolysis. Chronic cases occur more commonly and present with extravascular haemolysis. Venous thromboembolism may occur in many patients.
- Diagnosis is based on evidence of haemolysis, spherocytes and macrocytes in peripheral blood and positive direct and indirect Coombs' tests. In some cases, autoimmune thrombocytopenia may also be present along with haemolysis (*Evan's syndrome*).
- Exclude underlying systemic lupus erythematosus, lymphoma and leukaemia.

Coombs' Test

- In direct Coombs' test (direct antiglobulin test), patient's red cells are washed and suspended in saline. Rabbit antihuman globulin is added. Agglutination of red cells indicates the presence of antibodies on the surface of red cells.
- In indirect Coombs' test, normal red cells and rabbit antihuman globulin are added to the patient's serum. This produces agglutination of red cells if antibodies are present in the serum.

Treatment

- Prednisolone 60 mg daily initially for first 2–4 weeks, followed by gradual tapering. When a dose of 20 to 30 mg daily of prednisone in an adult is achieved, with a persistent remission, as indicated by the stable haemoglobin level and decreasing reticulocyte count, it is recommended that alternate day prednisone doses be commenced.
- Patients with particularly rapid haemolysis may require intravenous methylprednisolone at a dose of 250 to 1000 mg/day for 1 to 3 days.
- Blood transfusion is avoided as far as possible, but may be used as a temporising measure in critically ill patients. Due to the presence of autoantibodies, it may be difficult to get cross-matched blood. In such situation, it is best to use ABO- and Rh-compatible blood under the cover of intravenous hydrocortisone.
- Danazol can be used in association with prednisone as first-line therapy allowing for a shorter duration of prednisone therapy.
- Splenectomy in patients who have not had a satisfactory response to initial corticosteroids, who relapse after having responded, or require the equivalent of more than 10 to 15 mg prednisone per day to maintain an acceptable haemoglobin level.
- Intravenous immunoglobulin for patients refractory to conventional therapy with corticosteroids; may also be used as a possible temporising measure before doing a splenectomy.
- Rituximab:
  - A humanized monoclonal antibody directed against CD20 on pre-B cells and mature B lymphocytes..
  - Useful in refractory cases.
  - Also useful in secondary type of warm AIHA.
  - Adverse effects include hypotension, fever, chills, rigors, hypertension, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, cardiogenic shock.
  - Contraindicated in untreated hepatitis B infection.
- Immunosuppression with azathioprine, cyclophosphamide, cyclosporine and others in patients unresponsive to rituximab and splenectomy.

Cold Haemagglutinin Disease or Cold Agglutinin Disease

- Cold haemagglutinin disease (CHAD) is characterised by haemolytic anaemia of varying severity. This results from autoantibodies that act as red cell agglutinins at low temperatures.
- After exposure to cold, the patient develops acrocyanosis as a result of red cell autoagglutination.
- CHAD is termed 'primary' if no malignant or infectious disease can be found by clinical and radiological assessment.
- Anti-I antibodies are associated with primary cold autoimmune hemolytic anaemia, as well as *Mycoplasma pneumoniae* and lymphoma. Anti-i is associated with haemolysis caused by infectious mononucleosis or lymphoma.
- Patients are advised to avoid cold exposure.
- Rituximab is useful in acute symptomatic cases while chlorambucil and cyclophosphamide in more severe chronic cases.
- Splenectomy and glucocorticoids are not much useful
- Post-infectious cases are often self-limited.

Paroxysmal Cold Haemoglobinuria (Donath-Landsteiner Syndrome)

- Paroxysmal cold haemoglobinuria (PCH) is characterised by attacks of acute haemolysis and haemoglobinuria on exposure to cold. This results from autoantibodies (IgG type) that act as red cell lysins at low temperatures. Other features include aching pains, abdominal cramps, headache, often followed by chills and fever.

Drug-Induced Immune Haemolytic Anaemia

- Drugs produce immune haemolysis by two mechanisms:
  - Drug-independent antibodies are induced by some drugs that produce subtle alteration in red cell membrane. This results in haemolysis identical to warm AIHA. There is extravascular haemolysis with positive direct Coombs' test. This commonly occurs with α-methyldopa, cladribine and fludarabine. Can continue for several weeks after cessation of offending drug.
  - Drug-dependent antibodies can be categorised into two subtypes:
    - Hapten type which is due to non-covalent binding of drug to the RBC which is then targeted by autoantibody (e.g. penicillins)
    - Drug-autoantibody immune (ternary) complexes leading to complement-dependent haemolysis (e.g. quinidine).

Q. What are myeloproliferative diseases or myeloproliferative neoplasms?

- Myeloproliferative diseases (now known as myeloproliferative neoplasms) occur due to clonal expansion of a multipotent haematopoietic progenitor cell with the overproduction of one or more of mature, functional elements of the blood (peripheral blood granulocytosis, thrombocytosis or erythrocytosis alone or in combination) with no dyserythropoiesis, granulocytic dysplasia or monocytosis.
- These conditions may evolve into acute leukaemia.
- Following conditions are included under this category of diseases:
  - Polycythaemia vera.
  - Idiopathic myelofibrosis or primary myelofibrosis.
  - Essential thrombocytosis.
  - Chronic myeloid leukaemia or chronic myelogenous leukaemia (associated with *BCR-ABL1* genetic abnormality).
  - Others: Chronic neutrophilic leukaemia (CNL), chronic eosinophilic leukaemia-not otherwise classified (CEL-NOS), mastocytosis and myeloproliferative neoplasm, unclassifiable (MPN-u).

Q. Classify myeloid neoplasms.

- The term 'myeloid' includes all cells belonging to the granulocytic (neutrophil, eosinophil, basophil), monocyte/macrophage, erythroid, megakaryocytic, and mast cell lineages.
- Myeloid neoplasms include five major entities:
  - Acute myeloid leukaemia (AML).
  - Myelodysplastic syndromes (MDS).
  - Myeloproliferative neoplasms (MPN).
  - Myelodysplastic/Myeloproliferative neoplasms (MDS/MPN) overlap.
  - Myeloid neoplasms associated with eosinophilia and specific molecular abnormalities.

Q. What is polycythaemia? How do you classify polycythaemia?

Q. What are the clinical manifestations of polycythaemia?

- Polycythaemia signifies an increase in the number of red blood cells above normal in the circulating blood. The increase may or may not be associated with an elevation in the total quantity of red blood cells in the body.
- In relative polycythaemia, the concentration of the red cells becomes greater than normal (but total red cell mass is normal) in the circulating blood. This occurs as a result of loss of blood plasma.
- In absolute polycythaemia, there is an increase in the total red cell mass. It is of two types:
  - Primary polycythaemia (erythraemia; polycythaemia vera; primary proliferative polycythaemia) denotes absolute polycythaemia of unknown aetiology. This is associated with decreased EPO levels.
  - Secondary polycythaemia (erythrocytosis) denotes absolute polycythaemia of known aetiology (which occurs in response to some known stimulus). This is associated with increased EPO levels.

Classification and Causes

Relative polycythaemia (reduced plasma volume, normal red cell mass).

- Dehydration—low fluid intake, vomiting, diarrhoea, sweating, acidosis.
- "Stress" polycythaemia.

Absolute polycythaemia (increased red cell mass).

- Primary polycythaemia (erythraemia; polycythaemia vera).
- Secondary polycythaemia (erythrocytosis)—causes given below.

Increased production of EPO as a consequence of central hypoxia	*Increased production of EPO as a consequence of local renal hypoxia*
• High altitude	• Renal artery stenosis
• Cyanotic congenital heart diseases (TOF—tetralogy of Fallot, Eisenmenger's complex)	• End-stage renal disease
	• Hydronephrosis
• Pulmonary diseases (e.g. COPD—chronic obstructive pulmonary disease)	• Renal cysts (polycystic kidney disease)
	• Post-renal transplant erythrocytosis
• Sleep apnoea syndrome	
• Chronic carbon monoxide poisoning	
• Smokers	
• Abnormal haemoglobins with high oxygen affinity	
Increased production of EPO as a consequence of drugs	*Increased production of EPO or EPO-like substance by tumours*
• EPO administration	• Cerebellar haemangioblastoma
• Androgen administration	• Renal tumours (carcinoma, adenoma, sarcoma)
	• Uterine myoma, hepatocellular carcinoma, phaeochromocytoma

Clinical Features

- The clinical features of polycythaemia include a characteristic "ruddy" cyanosis, dizziness, headache, epistaxis and an increased incidence of thrombotic complications. In addition, clinical manifestations of the underlying disease will be present in secondary forms.

Q. Discuss the clinical features, diagnosis and management of polycythaemia vera.

Definition

- Polycythaemia vera is a clonal stem-cell disorder characterised by an increased production of all myeloid elements; however, the disease is generally dominated by an elevated haemoglobin concentration.
- Haematocrit >60 in males and >56 in females.
- Gradual in onset and runs a chronic slowly progressive course.
- It is one of the chronic myeloproliferative disorders.

Aetiology

- Unknown; however, hypersensitivity to interleukin-3 may play a role.

Clinical Features

- Predominantly seen in people over the age of 40 and more common in males.
- Complaints related to increased viscosity and/or decreased cerebral perfusion include headache, dizziness, vertigo, a sense of fullness in the head, rushing in the ears, visual disturbances, tinnitus, syncope and even chorea.

- Pruritus, particularly after bathing is frequent and may be disabling.
- The patients often have a high colour, suffused conjunctivae, deep red palate, dusky red hands and retinal venous engorgement.
- Splenomegaly is very common, and symptoms related to it may be present. Hepatomegaly occurs in 30% cases.
- Symptoms of peripheral vascular insufficiency, and thrombotic and haemorrhagic complications.
- Incidence of peptic ulcer is five times higher in patients with polycythaemia vera.
- Bleeding manifestations like epistaxis, bleeding from peptic ulcer, intramuscular haemorrhages and bruising.
- Hyperuricaemia may result in the formation of urate stones and uric acid nephropathy.

Diagnosis

- Haemoglobin concentration and haematocrit are markedly elevated. However, in many patients, the plasma volume is also elevated that results in near-normal haematocrit. Hence, it is important to determine the red cell mass.
- Increased red cell mass and blood viscosity. Red cell mass is reliably determined by isotope dilution using the patient's ^{51}Cr-tagged red cells.
- Total white cell count and platelet count are usually elevated.
- Absolute basophil count is increased to $>100/\mu L$ in majority.
- The arterial oxygen saturation is normal in contrast to hypoxic erythrocytosis where it is reduced. Patients with high-affinity haemoglobin also have normal oxygen saturation.
- Bone marrow shows either erythroid hyperplasia or panhyperplasia and depletion of iron stores.
- Urine and serum levels of EPO are reduced.
- Leucocyte alkaline phosphatase (LAP), serum vitamin B_{12} levels and B_{12} binding capacity are increased in majority.
- Abnormal liver function tests and increased urate levels.
- Janus kinase 2 (*JAK2*) mutations (seen in 95% patients with polycythaemia vera, and in 50% cases of essential thrombocytosis and primary myelofibrosis).

Janus Kinases

- A tyrosine kinase family comprising four members, JAK1, JAK2, JAK3 and TYK2, which are utilised by haematopoietic growth factors and cytokine receptors to phosphorylate tyrosine residues on specific intracellular proteins after the interaction of the receptor with its ligand.
- Located on chromosome 9.
- JAK2 is used by the EPO, thrombopoietin and G-CSF receptors to transmit signals and thus is integrally involved in haematopoiesis.
- JAK2 inhibitors are may be useful for managing these patients.

Diagnostic Criteria

Major criteria	Minor criteria
1. Haemoglobin >18.5 g/dL (men) or >16.5 g/dL (women) OR Haemoglobin or haematocrit >99th percentile of reference range for age, sex or altitude of residence OR Haemoglobin >17 g/dL (men) or >15 g/dL (women) if associated with a documented and sustained increase of >2 g/dL from baseline that cannot be attributed to correction of iron deficiency OR Elevated red cell mass >25% above mean normal predicted value 2. Presence of *JAK2V617F* (a mutation in *JAK2*) or similar mutation	1. BM showing hypercellularlity for age and trilineage growth (panmyelosis) 2. Subnormal serum EPO level 3. Endogenous erythroid colonies growth

Diagnostic criteria

Both major criteria + 1 minor criterion OR first major criterion + 2 minor criteria

Complications

- Thrombotic episodes.
- Peptic ulcer.
- Hyperuricaemia.
- Sudden massive increase in splenic size.
- Myelofibrosis and myeloid metaplasia.
- Acute leukaemia.
- Erythromelalgia.

Treatment

- It has a very slow course. Aim of therapy is to maintain haematocrit below 45 in males and 42 in females.
- Repeated venesection (phlebotomy) is the treatment of choice.
- Alkylating agents and ^{32}P (phosphorus) should be avoided as these agents are leukaemogenic.
- Consider a cytotoxic agent if the patient is intolerant to venesection, thrombocytosis occurs, or symptomatic or progressive splenomegaly develops. Hydroxyurea is the agent of choice in all patients. If it fails, interferon-α is used. In elderly patients (>70 years), ^{32}P or busulphan may still be useful.
- Low dose aspirin in all patients to reduce thrombotic episodes.
- Anagrelide (inhibitor of platelet aggregation) may be used if the patient continues to have thrombotic features despite above treatment.
- Asymptomatic hyperuricaemia does not require treatment unless chemotherapy is planned.
- Generalised pruritus should initially be treated with antihistamines. If these agents do not help, hydroxyurea, interferon-α and psoralens with UV light in "A" range (PUVA) may be tried.

Q. How will you differentiate primary polycythaemia (polycythaemia vera) from secondary polycythaemia with hypoxia [e.g. chronic obstructive pulmonary disease (COPD)]?

Differentiating feature	Primary	Secondary
• Oxygen saturation	Normal	Low
• Erythropoietin levels	Decreased	Increased
• Total white cell count	Increased	Normal
• Absolute basophil count	Increased	Normal
• Platelet count	Increased	Normal
• Leucocyte alkaline phosphatase (LAP)	Increased	Normal
• Vitamin B$_{12}$ levels	Increased	Normal
• Bone marrow	Panhyperplasia	Erythroid hyperplasia
• Splenomegaly	Present	Absent

Q. Discuss the causes, clinical features and management of agranulocytosis.

- Normal absolute neutrophils counts is greater than 1500/mm^3.
- A reduction in number of circulating neutrophils below 1500/mm^3 is known as neutropenia.
- Severe neutropenia means neutrophil count below 500/mm^3. These patients are at risk of developing serious infections.
- Agranulocytosis indicates neutrophil count below 100/mm^3.

Causes of Neutropenia

Reduced neutrophil production	Increased neutrophil destruction
Marrow infiltration	• Hypersplenism
• Leukaemias	• Severe sepsis
• Myelodysplastic syndrome	• Antineutrophil antibodies
• Myelofibrosis	• Systemic lupus erythematosus
• Granulomatous infiltration (e.g. tuberculosis, histoplasmosis)	• Felty's syndrome
	• Medications (phenylbutazone, phenothiazines)

Marrow injury	**Miscellaneous causes**
• Drugs [chloramphenicol, antithyroid drugs, non-steroidal anti-inflammatory drugs (NSAIDs), alkylating agents, antimetabolites, sulpha drugs, penicillins, carbamazepine] • Infections (typhoid, malaria, viral hepatitis, kala-azar, infectious mononucleosis, measles, brucellosis, HIV) • Aplastic anaemia • Paroxysmal nocturnal haemoglobinuria • Radiation	• Vitamin B_{12} deficiency • Folic acid deficiency • Cyclical neutropenia

Clinical Features

- History of exposure to one of the agents.
- Sore throat, fever with chills and rigors.
- Necrotic ulcers in throat and mouth.
- Other infections include cellulitis, sinusitis, otitis, pneumonia, perirectal infections, etc. Bacterial infections generally involve *Staphylococcus aureus, Staphylococcus epidermidis*, streptococci, enterococci, *Pseudomonas aeruginosa*, and other Gram-negative bacilli. Fungal infections usually arise from *Candida* or *Aspergillus* species.
- Toxaemia and septicaemia later lead to death.
- Bleeding manifestations if the patient has associated thrombocytopenia or develops DIC due to sepsis.
- "Cyclic neutropenia", most often an autosomal dominant disorder is neutropenia occurring in cycles of 3–4 weeks.

Investigations

- Total leucocyte count is markedly decreased.
- Reduction or absence of neutrophils in the peripheral blood.
- In many, the bone marrow shows a virtual disappearance of the granular cells and their precursors. In some, the marrow shows an arrest of maturation.
- Evidences of other diseases, e.g. leukaemia, and myelodysplastic syndrome.
- Vitamin B_{12} and folate levels
- Cultures of various body fluids to find possible organisms causing infection.
- Radiographs and ultrasound to localise the site of infection.

Treatment

- Removal of offending agent.
- Barrier nursing.
- If febrile, initiate broad-spectrum antibiotics covering gram-negative organisms within first hour of presentation. Monotherapy with piperacillin/tazobactam, meropenem or imipenem/cilastatin as initial empirical antibiotic treatment is recommended at present. Addition of vancomycin to cover for gram-positive organisms is usually not recommended empirically unless patient has a high risk (e.g. haemodynamic instability or other evidence of severe sepsis, pneumonia documented radiographically, clinically suspected catheter-related infection, skin or soft tissue infection at any site or severe mucositis).
- Role of granulocyte transfusions is controversial. Transfused granulocytes have a short life. They may form aggregates that can produce pulmonary compromise. Further, there is a possibility of CMV transmission.
- Recombinant G-CSF and granulocyte–monocyte colony-stimulating factor (GM-CSF) are useful in high-risk patients as they shorten the period of recovery and the duration of infection. These should not be used before or 24 hours after administering cytotoxic chemotherapy. Adverse effects include skin rash, acute respiratory distress syndrome and myalgias.

Q. How do you classify leukaemias?

Acute	Chronic
• Lymphoid (lymphoblastic) • Myeloid (myelogenous)	• Lymphoid (lymphocytic) • Myeloid (myelocytic)

Subclassification of Leukaemias – FAB (French–American–British) Classification

Acute lymphoblastic	Acute myeloid
• Common type (pre B)—L1, L2 • T cell—L1, L2 • B cell—L3 • Undifferentiated (rare)	• M0 — Minimally differentiated leukaemia • M1 — Myeloblastic without maturation • M2 — Myeloblastic with maturation • M3 — Promyelocytic • M4 — Myelomonocytic • M5 — Monocytic • M6 — Erythroleukaemia (DiGugliemo's disease) • M7 — Megakaryocytic
Chronic lymphocytic	**Chronic myelocytic (myeloid)**
• B cell CLL—Common • T cell CLL (rare), e.g. T-cell granular lymphocytic leukaemia • Hairy cell leukaemia • B-cell prolymphocytic leukaemia (PLL)	• Ph.^{x} positive • Ph.^{x} negative, BCR^{xx} positive • Ph.^{x} negative, BCR^{xx} negative • Eosinophilic leukaemia

Ph.^{x} = Philadelphia chromosome
BCR^{xx} = Breakpoint cluster

WHO Classification of Acute Myeloid Leukaemia and Acute Lymphoblastic Leukaemia

Acute myeloid leukaemia	Acute lymphoblastic leukaemia*

• AML with recurrent genetic abnormalities (includes acute promyelocytic leukaemia)
• AML with MDS-related changes
• Therapy-related myeloid neoplasms
• AML, not otherwise specified
  • AML with minimal differentiation
  • AML without maturation
  • AML with maturation
  • Acute myelomonocytic leukemia
  • Acute monoblastic/monocytic leukemia
  • Acute erythroid leukemia
  • Acute megakaryoblastic leukemia
  • Acute basophilic leukemia
  • Acute panmyelosis with myelofibrosis
• Myeloid sarcoma
• Myeloid proliferations related to Down syndrome
• Blastic plasmacytoid dendritic cell neoplasm
	• Precursor lymphoid neoplasms
	• B-cell lymphoblastic leukemia/lymphoma,
	• B-cell lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
	• T-cell lymphoblastic leukemia/lymphoma

*ALL and lymphoblastic lymphoma are the same disease entities at the morphologic and immunophenotypic levels and classified as either B- and T-cell lymphoblastic leukemia/lymphoma

Q.   Discuss the aetiology of leukaemias.

- In majority of patients, the aetiology is unknown. However, in a minority of cases, some associations have been described.

Familial and genetic
- Identical twins
- Down's syndrome
- Ataxia telangiectasia
- Klinefelter's syndrome

Ionising radiation
- Atomic bombing
- Therapeutic irradiation
- X-rays of foetus in pregnancy

Drugs and toxins
- Cytotoxic drugs like alkylating agents, topoisomerse II inhibitors
- Exposure to benzene
- Chloramphenicol, phenylbutazone

Retroviruses
- Human T-cell leukaemia lymphoma virus (human T-cell lymphotropic type I virus)

Immunological
- Immune deficiency states

Q.   Define acute leukaemia. Discuss the clinical features, investigations and management of acute leukaemias.

Definition

- Acute leukaemia is characterised by a failure of cell maturation, proliferation of immature cells that fill up the bone marrow and ultimately spill over of these immature cells into the peripheral blood.

Acute Lymphoblastic Leukaemia

- Majority are B-cell leukaemias representing approximately 85% of all acute lymphoblastic leukaemias (ALLs).
- T-cell ALL is found more typically in adolescents and the NK-cell ALLs are more common in adults.

Acute Myeloid Leukaemia

- Occur due to a somatic gene mutation in myeloid cells that results in the loss of control at one level of production. This loss of control then leads to increased, decreased or normal levels of production of that line and disturbed production of other cell lines resulting from crowding or inhibitory suppression in the bone marrow.
- Besides quantitative disturbances, function of cells can be affected.

Clinical Features

- Both acute lymphoblastic (acute lymphocytic or acute lymphoid) and acute myeloblastic (acute myeloid) leukaemias share many clinical features in common. Patient often presents with non-specific "flu-like" symptoms.
- The symptoms and signs of acute leukaemias are due to one or more of the following:
  - Anaemia.
  - Granulocytopenia.
  - Thrombocytopenia.
  - Expanding cell mass in bone marrow.
  - Leukaemic infiltration of tissues.
  - Others.

Anaemia
- Pallor, tiredness, malaise.
- Cardiorespiratory symptoms in severe anaemia.

Granulocytopenia
- Fever due to septicaemia.
- Infections at various sites, the common sites being skin, gingiva, lung, peri-rectal area and urinary tract.

Thrombocytopenia

- Thrombocytopenia results in bleeding. The common sites of bleeding include gum, nose (epistaxis), skin (purpura, ecchymoses, petechiae, easy bruising), buccal mucosa, fundus and per vaginum.
- Intracranial bleeding is a serious and fatal complication. It is usually associated with headache, fundal haemorrhages and focal neurological deficits.

Expanding Cell Mass in Bone Marrow

- Bone pains.
- Sternal tenderness.

Leukaemic Infiltrations

- Infiltrations of various tissues by leukaemic cells can occur. Common sites of leukaemic infiltration are:
    - Leukaemic infiltration of liver, spleen and lymph nodes results in hepatosplenomegaly and generalised lymphadenopathy.
    - Involvement of the central nervous system results in leukaemic infiltration of brain parenchyma, spinal cord parenchyma and meninges ("leukaemic meningitis"). Leukaemic meningitis starts as headache and nausea. Papilloedema, cranial nerve palsies, seizures and altered consciousness develop as disease progresses. The cerebrospinal fluid characteristically shows leukaemic blast cells, elevated proteins and reduced glucose.
    - Mediastinal masses with T-cell ALL.
    - Other areas of leukaemic infiltration include mouth, gums (gingival hypertrophy; particularly common with M4 and M5 types), skin (leukaemia cutis), testes, ovaries, eyes and bone. Extramedullary masses of neoplastic myeloid precursor cells are known as chloromas.

Others

- Hyperleucocytosis (leucocyte counts >1,00,000/mm^3), usually seen in adult ALL and monocytic type of AML presents with fever, headache, stroke, intracranial haemorrhage, dyspnoea, chest pain, pulmonary infarction, acute respiratory distress syndrome, or disseminated intravascular coagulation (DIC). Patient may present with tumour lysis syndrome even without chemotherapy and requires urgent leucopheresis.
- DIC in acute promyelocytic leukaemia.

Investigations

- Severe anaemia of normochromic type.
- MCV is normal or raised.
- Total leucocyte count is markedly raised, but usually less than 100×10^9/L (range 1×10^9/L to 500×10^9/L). Leucopenia is also common particularly in AML.
- Peripheral smear shows numerous blast cells and other primitive cells.
- Auer rods in AML: Seen in peripheral smear within the leukaemic cells. They are seen as groups of rod-shaped red inclusions in the cytoplasm.
- Platelet count is markedly decreased.
- Bone marrow is hypercellular with replacement of normal elements by leukaemic blast cells.
- Other routine investigations include liver function tests, renal function tests, coagulation studies, plasma LDH and plasma uric acid.
- In ALL, a lumbar puncture is necessary to rule out occult CNS involvement.
- Immunophenotyping of leukaemic cells using flow cytometry is necessary for accurate diagnosis and to initiate risk-directed treatment. An extensive panel of monoclonal antibodies to cell surface "cluster of differentiation" (CD) markers is used.
- Cytogenetic and molecular genetic analysis of leukaemia cells are important for prognosis and treatment outcome.

Management

- The first and major decision to be taken is whether or not to give specific therapy. If specific therapy is not desired, the patient is only given supportive therapy.

Supportive Therapy

- Treatment of anaemia with red cell concentrate.
- Treatment of thrombocytopenic bleeding with platelet transfusions.
- Identification of the organism and appropriate antimicrobial treatment in bacterial, fungal, protozoal and viral infections.
- Barrier nursing.
- Continuous monitoring of hepatic, renal and haemostatic functions.
- Maintenance of fluid and electrolyte balance. In patients undergoing rapid lysis of leukaemic cells following chemotherapy, the occurrence of hyperuricaemia, hyperkalaemia, hypocalcaemia and hyperphosphataemia (tumour lysis syndrome) can be prevented by close attention to hydration, urine alkalinization and allopurinol before starting chemotherapy.
- For hyperleucocytosis, emergent reduction in leucocyte counts is done using chemotherapy or hydroxyurea, and leucopheresis (removal of circulating cells with re-infusion of leucocyte-poor plasma).
- Psychological support.

Bone Marrow Transplantation

- Bone marrow transplantation has to be considered in young patients under 40 years with acute myeloblastic leukaemia in first remission, and acute lymphoblastic leukaemia (ALL) in first, second or subsequent remission.

Specific Therapy

Acute Lymphocytic Leukaemia

- Specific therapy involves remission induction, CNS-directed treatment and consolidation, re-induction, and remission maintenance.
- The goal of induction therapy is to induce morphologic remission and to restore normal haematopoiesis and bone marrow showing normal cellularity with fewer than 5% blasts. Induction therapy consists of at least three systemic drugs—a glucocorticoid (usually dexamethasone or prednisolone), vincristine and L-asparaginase with or without daunorubicin, and intrathecal therapy (particularly in high-risk patient). It aims to induce complete morphologic response in 4–6 weeks.
- CNS-directed treatment and consolidation aims to prevent CNS relapses and to reduce systemic minimal residual leukaemic burden. CNS therapy involves weekly or biweekly intrathecal therapy (hydrocortisone, methotrexate and cytarabine) along with systemic drugs like high-dose methotrexate and 6-mercaptoputine. Cyclophosphamide, vincristine and cytarabine may also be used in consolidation phase. CNS-directed treatment may be added during induction therapy in high-risk patients.
- Re-induction or re-intensification (essentially similar to induction phase) reduces chances of relapse.
- Maintenance involves administering drugs for 2 years or more. It consists of daily 6-mercaptopurine and weekly methotrexate with or without pulses of vincristine and dexamethasone. Periodic intrathecal therapy is continued.

Acute Myeloid Leukaemia

- Includes induction and maintenance (post-remission) therapy.
- Candidates for allogenic stem cell transplantation should be identified early during induction phase. These include patients <70 years with high-risk karyotype (see "poor prognostic factors" below) who are in first remission after induction phase.
- Induction therapy includes an anthracycline (e.g. daunorubicin or idarubicin) and cytosine arabinoside ± etoposide.
- Patients achieving remission with induction therapy (blasts <5% in bone marrow, absolute neutrophil count >1000/mm³, platelets >100,000/mm³, and no extramedullary disease) should receive cycles of maintenance or post-remission therapy or allogenic stem cell transplantation. In young patients (<60 years), high-dose cytosine arabinoside is recommended.

Acute Promyelocytic Leukaemia (M3)

- It is associated with severe coagulation complications (DIC) and represents a medical emergency because of risk of catastrophic bleeding.

- It has a better prognosis and responds well to combination of induction therapy plus all-trans retinoic acid (ATRA; tretinoin). Treatment needs to be started as soon as diagnosis is suspected on the basis of presentation and bone marrow evaluation.
- In relapsed cases, arsenic trioxide has been found to be effective.
- While receiving ATRA, differentiation syndrome may occur which is characterised by dyspnoea, fever, weight gain, hypotension, pulmonary infiltrates, and pleural and pericardial effusion. Treatment is with dexamethasone.

Acute lymphocytic leukaemia

Induction therapy
- Dexamethasone or prednisolone + vincristine + L-asparaginase ± daunorubicin
AND
- Intrathecal therapy (in high-risk patients)

↓

CNS-directed and consolidation therapy
- High-dose methotrexate and 6-mercaptoputine (alternative agents: cyclophosphamide or cytosine arabinoside)
AND
- Intrathecal therapy (hydrocortisone, cytarabine, methotrexate)

↓

Re-induction or re-intensification therapy
- Similar to induction therapy

↓

Maintenance therapy
- Methotrexate + 6-mercaptopurine

Acute myeloid leukaemia

Remission—induction
Daunorubicin + cytosine arabinoside ± etoposide
OR
Idarubicin + cytosine arabinoside ± etoposide

↓

Complete remission

High-risk karyotype	High-risk, normal karyotype*	Low-risk, normal karyotype*	Low-risk karyotype [t(15;17), t(8;21), inv(16)]
Allogenic stem cell transplantation if available; otherwise investigational therapy	Allogenic stem cell transplantation OR Investigational therapy	3–4 cycles of high-dose cytosine arabinoside OR Autologous stem cell transplantation	3–4 cycles of high-dose cytosine arabinoside

*Low risk and high risk depend on other prognostic factors listed in the box

Poor Prognostic Factors

AML	ALL
• Age >60 years	• Age >60 years (in adults); in children, age <1 year or >9 years
• Secondary cause present	
• TLC >30,000/mm³ at presentation	• Male sex
• Presence of DIC	• TLC >50,000/mm³
• French–American–British (FAB) type M0, M5, M6, M7	• Mediastinal mass
	• CNS involvement
• Auer rod absent	• L3 type
• Fibrosis on bone marrow examination	• Pro-B or B-cell ALL (T-cell ALL in children)
• High-risk karyotype [t(6;9), inv(3)]	• Hypodiploidy (<45 chromosomes)
• Therapy-related leukaemia	

Q. How do you differentiate acute lymphoblastic leukaemia from acute myeloblastic leukaemia?

Clinical features	Acute lymphoblastic leukaemia	Acute myelogenous leukaemia
• Age group	Common in children	Common in adults
• Presentation as bleeding	Less common	More common (in 60%)
• Lymphadenopathy	More common	Less common
• Hepatosplenomegaly	In majority (50–75%)	In minority
• CNS involvement	More common	Less common
• Gum involvement	—	Gum hypertrophy common in M5 type
• Testicular involvement	In 10–20%	—
• Eye involvement	More common	Less common
Investigations		
• Leukaemic blasts	Lymphoblasts (10–15 μm) are smaller than myeloblasts, with a thin rim of agranular cytoplasm and round or convoluted nucleus	Myeloblasts (12–20 μm) are larger than lymphoblasts, with discrete nuclear chromatin and multiple nucleoli
• Cytoplasmic Auer rods	Not present	Present in 10–20% (diagnostic)
• Nuclear enzyme, terminal deoxynucleotidyl transferase (Tdt) in leukaemic blasts	In more than 90%	Rarely present
• Cytochemical staining		
• Myeloperoxidase	Negative	Positive
• Sudan black B	Negative	Positive
• Chloracetate esterase	Negative	Positive
• Periodic acid–Schiff (PAS)	Positive in >50% of cells	Positive in <25% of cells

Q. Describe subleukaemic leukaemia.

- In acute leukaemia, one would expect an increase in total leucocyte count.
- In a small percentage of patients with acute leukaemia, the total leucocyte count is normal or less than normal. Abnormal cells are seen in the peripheral blood. This is termed subleukaemic leukaemia.
- Diagnosis is confirmed from the bone marrow, which is replaced by leukaemic cells.

Q. Define aleukaemic leukaemia.

- In a patient with acute leukaemia, one would expect an increase in total leucocyte count and abnormal cells in peripheral blood.
- In about 10% of the patients with acute leukaemia, total leucocyte count is normal or less than normal and there are no abnormal cells in the peripheral blood. This is called aleukaemic leukaemia. Some patients may present with cutaneous involvement (aleukaemic leukaemia cutis).
- Diagnosis is confirmed from the bone marrow, which is replaced by leukaemic cells.

Q. Discuss briefly about leukaemoid reaction.

- Total leucocyte count >50,000/μL is termed as leukaemoid reaction. It is usually due to excess of neutrophils and their precursors but sometimes can be due to lymphocytosis (lymphocytic leukaemoid reaction).
- It reflects the response of the normal healthy bone marrow to various stresses. The stresses include a number of infections (including tuberculosis), acute haemorrhage, acute haemolysis, drugs (e.g. steroids, growth factors), haematological and non-haematological malignancies and various toxic states.

Neutrophilic Leukaemoid Reaction

- Peripheral smear shows mix of neutrophils, myelocytes, metamyelocytes, promyelocytes and even a few myeloblasts.
- The bone marrow shows proliferation of all the normal myeloid elements; in contrast, in acute leukaemia, the most immature elements predominate.
- LAP score is normal or increased.
- No absolute eosinophilia or basophilia (versus CML—see below).
- Philadelphia chromosome or *ABL-BCR* negative.
- Treatment of underlying disorder corrects the blood picture.

Q. Define and classify stem cells. Discuss their clinical applications.

- Stem cells are undeveloped cells capable of proliferation, self-renewal, conversion to differentiated cells and regenerating tissues.
- Three classes of stem cells: totipotent, multipotent and pluripotent.
  - A fertilised egg is considered totipotent because it has the potential to generate all the different types of cells in the body.
  - Stem cells that can give rise to a small number of different cell types associated with different organs are called multipotent. These cells can generate a viable embryo (including support tissues such as the placenta).
  - Pluripotent stem cells are those that can give rise to any type of cell in the body except those needed to develop a foetus. These cells give rise to cells derived from all three embryonic germ layers: endoderm, mesoderm and ectoderm.
- Stem cells that are able to differentiate into cell types beyond those of the tissues in which they normally reside are said to exhibit plasticity. For example, stem cells from the bone marrow can give rise to three major types of brain cells: astrocytes, oligodendrocytes and neurons. The neural stem cells can differentiate into blood cells and muscle tissue.
- Two main types of stem cells are embryonic and non-embryonic.

Embryonic Stem Cells

- Embryonic stem cells (ESC) are pluripotent because they can differentiate into all cell types.
- Derived from the inner cell mass of a blastocyst, which forms several days after an egg is fertilised.
- An ESC line is created by taking the ESC and placing the cells on a feeder layer of fibroblasts. The feeder layer assists in maintaining the ESC in an undifferentiated state or adult stem cells.

Non-Embryonic (Adult or Somatic) Stem Cells

- Non-embryonic stem cells (non-ESC), also known as adult stem cells because the cells are obtained from adults. These are multipotent because their potential to differentiate into cell types is more limited.
- Two types of stem cells: haemopoietic, which are committed to differentiate into blood cells (CD34 positive), and the less differentiated mesenchymal stem cells. Adult stem cells which undergo mesodermal lineage-specific differentiation to osteocytes, adipocytes, and chondrocytes are named as mesenchymal stem cells.
- Adult stem cells (SC) such as haematopoietic stem cells (HSC) in bone marrow, peripheral blood or cord blood are currently the only type of SC commonly used to treat human diseases.
- Besides bone marrow cells, other adult tissue sources for stem cells include the umbilical cord blood, peripheral blood, nose, muscle, liver, skin, brain, and retina and limbus of the eye.

Clinical Applications

Therapeutic

- Only non-ESC have been used clinically so far.
- Beneficial for blood disorders such as leukaemia, multiple myeloma and lymphoma, and disorders with defective genes such as severe combined immune deficiency.
- Other possible uses where clinical trials are ongoing include:
  - Ischaemic heart disease
    - Use of autologous stem cells from bone marrow and peripheral blood.
    - Cells injected either into the coronary arteries or directly into the myocardium.
    - Can differentiate into myocardial cells or new blood vessels.
  - Spinal cord lesions
  - Non-union of fractured bones
  - Parkinson's disease
  - Huntington's disease
  - Motor neuron disease
  - Alzheimer's disease
  - Muscular dystrophy
  - Type 1 diabetes.

Q. Give a brief account of haematopoietic stem cells.

Q. Write a short note on peripheral blood stem cell transplantation.

- Haematopoietic stem cell (HSC) transplantation refers to infusion of HSC from a donor to a recipient with the intention to re-populate or replace totally or partly the recipient's haematopietic system.
- HSC are self-renewing cells that can repopulate all the cell lineages in the blood. Immature haematopoietic progenitor cells (CD34+) are a surrogate measure of the stem cell dose in the transplant product.
- The major sources of haematopoietic stem cells for transplantation include bone marrow (discussed below), peripheral blood (peripheral blood stem cells) and cord blood.
- Stem cells obtained from the recipient (same person) are called autologous. Immunosuppressives are not required. However, there is no graft-versus-tumour effect and therefore, increased risk of disease relapse or progression compared to allogenic graft. Further, graft may be contaminated with tumour cells.
- Stem cells obtained from someone other than the recipient are termed allogenic. Three types of allogenic donors are syngenic, related and unrelated. When the donor is an identical twin, donation is termed syngenic.
- The key to successful allogenic transplantation is finding an HLA-matched donor because it decreases the risk of graft rejection and graft-versus-host-disease (GVHD).

Peripheral Blood Stem Cells

- Peripheral blood stem cell transplantation is defined as transplantation of stem cells derived from the peripheral blood of a donor to a recipient (allogenic) or from the patient's own blood (autologous).
- HSC circulate in the peripheral blood but are in a very low concentration (<0.1% of all nucleated cells). To increase their numbers, haematopoietic growth factor (G-CSF or GM-CSF) is administered for 4–5 days to the donor (for allogenic transplant) or to the patient during recovery from intensive chemotherapy (for autologous transplant). Apart from increasing number of cells, G-CSF causes release of proteases that degrade proteins anchoring stem cells to the marrow stroma, thereby causing release of HCS into peripheral blood.
- After treatment with growth factors, stem cells are collected from the blood by pheresis and are infused in the recipient.
- The cells are engrafted in the recipient after variable period. Engraftment means recovery of neutrophil count to >500/mm^3 for 3 consecutive days.
- Compared to bone marrow transplant, use of peripheral blood stem cells results in more rapid haematopoietic recovery. However, the risks of GVHD are still similar to those associated with bone marrow transplantation.

Cord Blood Stem Cells

- Cord blood is a good source of HSC with no risk to infant or mother. Contamination of cord blood with CMV and Ebstein–Barr virus is low due to poor transmission from placenta. However, the major limitation is that the number of cells that can be collected from cord blood is small and an adult might require multiple cord blood donors.

Indications

Non-malignant conditions

• Inherited metabolic disorders	Adrenoleucodystrophy, Hurler syndrome, metachromatic leukodystrophy, osteopetrosis
• Inherited immune disorders	Severe combined immunodeficiency, Wiskott–Aldrich syndrome
• Inherited red cell disorders	Pure red cell aplasia, sickle cell disease, β-thalassaemia
• Marrow failure states	Severe aplastic anaemia, Fanconi anaemia
• Autoimmune diseases (experimental)	Systemic sclerosis, severe systemic juvenile rheumatoid arthritis, lupus, multiple sclerosis

Malignant conditions
- Selected cases of acute and chronic leukaemias
- Plasma cell disorders
- Myelodysplastic syndrome (MDS)

Comparison among Bone Marrow, Peripheral Blood and Cord Blood Stem Cells

Characteristic	Source		
	Cord blood	Peripheral blood	Bone marrow
• Stem cell content	Low	Good	Adequate
• Risk of tumour cell contamination	Not applicable	Low	High
• HLA matching	Less restrictive	Close matching	Close matching
• Engraftment	Slowest	Fastest	Medium
• Risk of acute graft-versus-host disease (GVHD)	Lowest	High	High
• Risk of chronic GVHD	Lowest	Highest	Medium

Conditioning Regimens

- Often required in recipient before transplantation.
- Can be myeloablative or non-myeloablative (reduced intensity).
- Myeloablative regimens eliminate malignant cells so that transfused HSC can populate the bone marrow and grow.
- The aim of non-myeloablative regimen is to induce immunosuppression in recipient so that graft of donor cells can take place. It is less-toxic and can be performed in patients with mild organ dysfunction.
- Conditioning regimens can produce complications, generally within 30 days and include infections, nausea, vomiting, alopecia, mucositis and interstitial pneumonia. Another important early complication is veno-occlusive disease of liver where patient develops jaundice, ascites and tender hepatomegaly.
- Conditioning regimens can also lead to late complications including infertility, ovarian failure and second malignancies (AML and solid organ malignancies).

Q. Briefly outline bone marrow transplantation.

- It is a type of haematopoietic stem cell transplantation (see above).

Bone Marrow Transplantation

- Syngenic bone marrow transplantation, i.e. from identical twin donor
- Allogenic bone marrow transplantation, i.e. from non-identical donor
- Autologous bone marrow transplantation, i.e. the patient's own marrow is harvested to be given back again after intensive therapy

Allogenic Bone Marrow Transplantation

- Method of transplantation:
  - The recipient is suitably "conditioned" with chemotherapy and radiotherapy. Conditioning ablates patient's haemo-poietic and immunological tissues.
  - Healthy marrow from a donor (preferably histocompatible sibling) is injected intravenously into the conditioned patient. The injected cells "home" to the marrow and produce erythrocytes, granulocytes and platelets. This usually takes 3–4 weeks. To regain good lymphocyte function and immunological stability, it takes longer time, even up to 3 years or more.
- Common complications of bone marrow transplantation are infections, GVHD, interstitial pneumonitis and graft failure.

Infections

- Infections may develop during three different phases after transplantation.
  - In the first phase, infections occur due to neutropenia and damage to gastrointestinal mucosal barrier produced by conditioning agents. Source of infection is oral, skin and gastrointestinal flora.
  - Second phase occurs during GVHD where T-cell function gets impaired. Patients are prone to develop opportunistic viral and fungal infections.
  - Third phase occurs due to chronic GVHD where both B-cell and T-cell functions are impaired. Therefore, patients are prone to develop bacterial (including encapsulated organisms), as well as opportunistic viral and fungal infections.

Graft-Versus-Host Disease (GVHD)

- GVHD results from the cytotoxic activity of donor T lymphocytes that become sensitised to their new host, which they regard as foreign.
- Occurs in 50–80% of allogenic bone marrow transplantation and is the cause of high long-term morbidity and mortality. It can even occur in HLA-identical siblings.
- GVHD can occur in two forms:
  - Acute GVHD occurs within first 100 days of transplantation. It occurs due to production of cytokines by Th1 cells. HLA mismatch is one of the most important risk factor for it. Main targets are skin, liver and gut. It causes diarrhoea, hepatitis, cholestasis and exfoliative dermatitis. Treatment includes methotrexate, cyclosporin, antithymocyte globulin, corticosteroids, tacrolimus, mycophenolate mofetil and monoclonal antibodies against T cells.
  - Chronic GVHD occurs more than 100 days after transplantation. It may arise independently or may follow acute GVHD. It occurs due to Th2 type cytokine production. It clinically resembles a connective tissue disorder and presents with dermatosis, liver injury, pulmonary fibrosis, alteration in gastrointestinal mucosa and reduced salivary and lacrimal flow. Treatment includes cyclosporin and corticosteroids.

Q. Discuss the natural course, clinical features and investigations of chronic myeloid leukaemia. Give a brief account of the treatment.

Q. Write a brief note on Philadelphia chromosome.

Definition

- Chronic myeloid leukaemia is a myeloproliferative disease characterised by excessive proliferation of myeloid cells with fairly normal maturation.

Cytogenetics

- It is the result of a reciprocal translocation between the long arms of chromosomes 9 and 22 [t(9:22)], cytogenetically evident as the Philadelphia chromosome (Ph). 5% patients are negative for Ph chromosome but have a complex translocation involving additional chromosomes but resulting in the same BCR-ABL 1 fusion gene.
- The fragment of chromosome 9 that joins the breakpoint cluster (*BCR*) of chromosome 22 carries Abelson (*ABL 1*) protooncogene (9.22). This fusion gene codes for a protein with tyrosine kinase activity. Increased and unregulated activity of tyrosine kinase can cause increase in tumour cell proliferation and growth, induce antiapoptotic effects, and promote angiogenesis and metastasis.
- Ph chromosome is also found in about 20% of adults with acute precursor B-cell lymphoblastic leukaemia, 5–10% of childhood ALL, and about 1 percent of adult AML.

Natural Course

- The disease has three phases:
  - Chronic stable phase lasts for 3–5 years.
  - Accelerated phase.
  - Blast crisis phase in which it transforms into acute myeloid or lymphocytic leukaemia.

Chronic Stable Phase

- Peak incidence in fourth and fifth decades, average age 55 years.

Symptoms

- Many patients are asymptomatic early on and disease may be diagnosed on routine blood examination.
- Symptoms are due to massive splenomegaly like abdominal distension, post-prandial fullness, reflux oesophagitis, dyspnoea and dragging discomfort in the left hypochondrium.
- Symptoms results from hypermetabolic state like fever, weight loss, sweating and heat intolerance.
- Symptoms of anaemia like fatigue, weakness and anorexia.
- Priapism.
- Bleeding tendencies, mainly due to platelet dysfunction occur late.

Signs

- Mild anaemia.
- Hepatomegaly.
- Moderate to massive, non-tender splenomegaly. Tenderness of spleen and splenic friction rub indicate splenic infarction.

Investigations in Chronic Stable Phase

- Normocytic normochromic anaemia.
- Total leucocyte count is markedly raised, almost always more than 20,000/μL, often exceeding 200,000/μL.
- Peripheral smear (blood picture) examination:
  - Full range of granulocyte precursors ranging from myeloblasts, myelocytes, metamyelocytes to mature neutrophils are seen. The mature forms predominate.
  - Myeloblasts are less than 5–10%, typically <2%.
  - Increase in basophils (<20%) and eosinophils.
  - Few nucleated red blood cells may be seen.
  - Platelet count may be normal, increased or decreased. Automated machines may give falsely elevated platelet counts due to disruption of granulocytes.
- Bone marrow study:
  - Hypercellular bone marrow with marked proliferation of all granulocytic elements.
  - 20–30% of the patients have mild bone marrow fibrosis in late stages.
- Philadelphia chromosome (Ph) is positive in more than 95% of cases, in all three phases.
- In Ph negative cases, evidence of translocation can be established by cytogenetics, reverse transcription-polymerase chain reaction (RT-PCR) and fluorescence *in situ* hybridisation (FISH).
- BCR–ABL rearrangement in peripheral blood or bone marrow.
- LAP score is very low, usually less than 5 (normal 20–100).
- Serum vitamin B_{12} levels are markedly raised due to increase in transcobalamin present in neutrophil granules.
- Serum LDH and uric acid levels are raised.
- Marked thrombocytosis may elevate serum potassium spuriously as platelets release potassium during clotting.
- Blood sugar may be falsely reduced due to glucose uptake and metabolism by leucocytes.

Treatment for Chronic Stable Phase

Chemotherapy

- The drugs available till recently did not produce cure (disappearance of Ph chromosome or BCR–ABL) in most patients.
- However, imatinib mesylate became available in 2001 and has been recommended in patients with chronic disease, accelerated phase and even in blast crisis.

- Other drugs that are used in chronic phase are hydroxyurea and busulphan. Hydroxyurea is used only to reduce leucocyte count initially. Busulphan is not often used.
- Chemotherapy is initiated with an induction dose, followed by a maintenance dose indefinitely.

Drug	Induction	Maintenance
• Imatinib	300–400 mg/day	300–400 mg/day
• Hydroxyurea	0.5–2.0 g/day	0.5–2.0 g/day
• Busulphan	4 mg/day	2–4 mg/day

Imatinib Mesylate

- Imatinib provides targeted therapy, i.e. high specificity for the tumour cells, providing a broader therapeutic window with less toxicity.
- It is an inhibitor of tyrosine kinase activity of BCR–ABL proteins producing apoptosis of cancer cells.
- In chronic stable disease, imatinib can produce complete haematological response in >95% cases and complete cytogenetic response in as many as 75% cases.
- Despite complete cytogenetic response, residual disease remains detectable in majority of the cases, suggesting that it fails to eradicate the abnormal stem cells.
- Resistance to imatinib mesylate results from overexpression of the BCR–ABL gene or genetic alteration.
- Side effects include fluid retention, nausea, muscle cramps, diarrhoea, skin rash, liver toxicity, bone pains and myelosuppression. Therapy is stopped if severe neutropenia or thrombocytopaenia develops; after recovery, dose reduction is considered.
- If a patient fails to respond to imatinib, other tyrosine kinase inhibitors (dasatinib and nilotinib) may be used. These have also been used as first-line drugs in treatment of CML.

Recombinant Interferon-α

- Can induce remission and maintain control in chronic stable phase. It is not effective in accelerated phase or blast crisis phase.
- Dose is 3–9 mega units/day intramuscularly or subcutaneously.
- May be combined with cytosine arabinoside.
- No role as a single agent in most patients; should be considered in cases unresponsive to imatinib and other tyrosine kinase inhibitors.
- rINF-α brings about:
  - Decrease in bone marrow cellularity.
  - Reduction in number of Philadelphia positive cells in 20% of cases.
  - Elimination of Philadelphia chromosome in 5% of cases.
  - Reduction in platelet count when it is very high.
- Side effects include flue-like syndrome, weight loss, fatigue, nausea, vomiting and headache.

Splenectomy

- Splenectomy is done to relieve the symptoms resulting from the massive size of spleen and in repeated splenic infarctions.

Bone Marrow Transplantation

- Indicated in patients under the age of 35 years who have a suitable donor.
- Best results are obtained when the transplantation is done in early chronic stable phase.
- It can result in permanent disappearance of the Ph-positive clone and hence can cure CML in early stages.

Recommendations on treatment

- Imatinib mesylate (400 mg/day) in newly diagnosed cases who are in chronic phase
- If response is suboptimal, consider a dose increase of imatinib or allogenic haematopoietic stem cell transplantation or rINF-α
- Failure is defined as:
  - No haematological response at 3 months
  - Incomplete haematological response at 6 months
  - No cytogenetic response at 6 months
  - Incomplete cytogenetic response at 12 months (Philadelphia chromosome–positive >35%)

Monitoring of Therapy

- The first step is the haematologic response (WBC <20,000/μL, platelet count <4,50,000/μL, no immature granulo-cytes in peripheral smear and spleen non-palpable) along with some cytogenetic response (Ph ≤35% and/or BCR-ABL ≤10%) within first 3 months.
- The second step is the complete cytogenetic response (no Ph+ metaphases and/or less than 1% BCR-ABL positive nuclei by FISH) at 6 months.
- The third step is the major molecular response (BCR-ABL≤0.1%) on peripheral blood at 12 months.
- Once major molecular response has been achieved, response can be assessed by real-time quantitative polymerase chain reaction (RT-Q-PCR) every 3 to 6 months.

Accelerated phase of chronic myeloid leukaemia

If not treated, chronic myeloid leukaemia may transform itself to a blastic phase with or without going through an accelerated phase after 1–5 years of onset. Features of accelerated phase are the following:

- Development of anaemia
- Refractoriness to therapy
- Increase in splenic size
- Increase in total leucocyte count with an increase in circulating immature cells, resembling "subacute" leukaemia (blasts 15–29%)
- Increase in basophil count (>20%)
- Thrombocytosis unresponsive to therapy or thrombocytopenia unrelated to chemotherapy
- Hydroxyurea along with one of the tyrosine kinase inhibitors are the most effective drug in accelerated phase
- Stem cell transplantation--once reversion to chronic phase or remission is achieve

Blast crisis phase of chronic myeloid leukaemia

Blast crisis phase represents the transformation of CML into an acute leukaemia
- "Myeloid blast crisis" occurs in 70% when the disease transforms into acute myeloblastic leukaemia
- "Lymphoid blast crisis" occurs in 30% when the disease transforms into acute lymphoblastic leukaemia

Features of blast crisis are the following:

- Refractoriness to treatment
- Abrupt increase in splenic size
- Bone pain and sternal tenderness
- Anaemia and bleeding tendencies
- Generalised lymphadenopathy
- Peripheral smear and bone marrow showing >30% blast cells simulating acute leukaemia
- Thrombocytopenia

Treatment of myeloid blast crisis is tyrosine kinase inhibitor with or without combination chemotherapy followed by stem cell transplantation in eligible patients.

Treatment for lymphoid blast crisis is same as for acute lymphoblastic leukaemia.

Q.   Discuss the clinical features, investigations and management of primary myelofibrosis (agnogenic myeloid metaplasia, myelofibrosis with myeloid metaplasia).

Q.   Define myelophthisis and discuss its causes.

Definitions

- Primary myelofibrosis is a myeloproliferative neoplasm which has the worst prognosis among the Philadelphia chromosome negative myeloproliferative neoplasms.
- Primary myelofibrosis is a clonal disorder of a multipotent haematopoietic progenitor cell characterised by increased fibrosis within the marrow, splenomegaly and extramedullary haemopoiesis. The extramedullary haemopoiesis can always be demonstrated in the spleen, usually in the liver and at times in lymph nodes, kidneys and adrenals.
- It can arise from antecedent polycythaemia vera or essential thrombocytosis.

Clinical Features

- Most cases occur after 60 years of age.
- A significant number of patients develop acute myeloid leukaemia.

Symptoms

- Symptoms of anaemia like fatigue, weakness and anorexia.
- Symptoms due to massive splenomegaly like abdominal distension, post-prandial fullness, reflux oesophagitis, dyspnoea and dragging discomfort in the left hypochondrium.
- Symptoms resulting from hypermetabolic state like fever, weight loss, sweating and heat intolerance.
- In late stages, bleeding tendencies due to thrombocytopenia.
- Death occurs due to portal hypertension and infections, with median survival around 5 years.

Signs

- Massive splenomegaly and hepatomegaly.
- Anaemia, lymphadenopathy, ascites, cardiac failure, jaundice and bleeding manifestations.
- Extramedullary haematopoiesis can also produce paraspinal masses with spinal cord compression, ascites, and pleural and pericardial effusion.

Investigations

- Haemoglobin is normal in the early stages, but markedly reduced in the late stages.
- Total leucocyte count may be normal, increased (early stages) or decreased (late stages).
- Platelet count is elevated in the early stages, but reduced in the late stages.
- Peripheral smear is diagnostic:
    - Leucoerythroblastic blood picture (precursors of granulocytes and erythrocytes being present simultaneously).
    - Many teardrop cells.
    - Anisocytosis and poikilocytosis.
    - Other features include many nucleated red blood cells, giant platelets with vacuoles, basophilic stippling and blasts up to 5–10%.
- Bone marrow examination is diagnostic. Atypia of megakaryocyte proliferation even in the absence of overt reticulin fibrosis is diagnostic but the bone marrow findings are variable.
    - At one end of the spectrum (early stage or "cellular phase"), the marrow is hypercellular with an increase in all three cell lines, particularly megakaryocytes. Fibrosis is minimal.
    - At the other end of the spectrum (late stage or "hypocellular phase"), the marrow is hypocellular with reduction in all the three cell lines. The marrow is densely filled with fibrous tissue.
- LAP score is elevated.
- Philadelphia chromosome or BCR-ABL negative.
- Mutation in JAK2 gene (seen in 50–60% cases).
- Serum vitamin B_{12} concentration is moderately elevated.
- Radiological examination reveals an increase in bone density of vertebrae and proximal ends of long bones.

Treatment

- Main goals of therapy are prolongation of survival and, if possible, cure by stem cell transplantation.
- If prolongation of survival or cure is not possible, symptom-orientated palliation is the main goal.

Treatment of Anaemia

- Correct other causes of anaemia.
- Red cell transfusions.
- Folic acid 5 mg daily.
- Corticosteroids (prednisolone) to control any autoimmune haemolysis.
- Danazol in combination with erythropoiesis-stimulating agents (e.g., EPO) may be effective in controlling anaemia in some patients.

- Another option is to give thalidomide (50 to 200 mg/day) or lenalidomide with prednisolone. This can control anaemia and splenomegaly in a substantial number of patients.

Treatment of Splenomegaly

- Hydroxyurea is useful to control splenomegaly. Can lead to myelosuppression that further exacerbates underlying anaemia.
- Busulphan 2 mg daily in elderly patients with cellular bone marrow and marked leukocytosis who do not respond to hydroxyurea.
- Splenectomy in selected cases.
- Local radiotherapy to reduce splenic size. It is reserved for patients who cannot undergo splenectomy for any reason, but the efficacy of this therapy is poor, and subsequent cytopenias are often severe.
- Intravenous cladribine in massive splenomegaly.

Bone Marrow Transplantation

- Allogenic bone marrow transplantation is the only curative treatment. It can be performed only in a limited number of cases as most are above 60 years.

Miscellaneous

- Allopurinol to control hyperuricaemia.
- Radiation therapy for extramedullary haematopoiesis
- Etanercept (TNF-α antagonist) for severe constitutional features.
- Ruxolitinib, a JAK2 inhibitor has been approved for use in high-risk cases.

Prognosis

- Median survival is 27 months to 135 months depending on presence of poor prognostic factors.
- Poor prognostic factors include:
  - Age >65 years.
  - Haemoglobin <10 g/dL.
  - Leucocytes >25,000/mm^3.
  - Circulating blasts. ≥1%.
  - Platelets <1,00,000/mm^3
  - Presence of constitutional symptoms.

Myelophthisis

- Myelophthisis is infiltration of marrow by non-haematopoietic or abnormal cells. Marrow fibrosis often occurs.

Causes of Myelophthisis or Other Causes of Myelofibrosis (which may also produce splenomegaly)

Malignant conditions	Non-malignant conditions
- Acute leukaemia (lymphocytic, myeloid)	- HIV infection
- Multiple myeloma	- Tuberculosis
- Chronic myeloid leukaemia	- Exposure to thorium dioxide
- Hairy cell leukaemia	- Systemic lupus erythematosus
- Polycythaemia vera	- Renal osteodystrophy
- Carcinoma metastatic to marrow	- Hyperparathyroidism
- Hodgkin's lymphoma	
- Lymphoma	
- Essential thrombocytosis	

Q. How do you differentiate chronic myeloid leukaemia from myelofibrosis?

Chronic myeloid leukaemia	Myelofibrosis
• Total leucocyte count markedly raised usually more than 20,000/μL	• Total leucocyte count may be raised, but usually less than 20,000/μL
• Peripheral smear shows full range of granulocyte precursors, predominantly mature forms	• Peripheral smear shows leucoerythroblastic blood picture, tear drop cells and anisopoikilocytosis
• Nucleated red cells few or absent	• Nucleated red cells numerous
• Thrombocytopenia occurs late	• Thrombocytopenia common
• Marrow fibrosis uncommon and minimal	• Marrow fibrosis common and dense
• LAP score is very low, usually <5	• LAP score is high, usually >100
• Philadelphia chromosome positive	• Philadelphia chromosome negative
• Very high vitamin B_{12} levels	• Moderate elevation of vitamin B_{12} levels

Q. Describe the aetiology, classification, clinical features, diagnosis and treatment of myelodysplastic syndrome (MDS).

- A subtype of myeloid neoplasms.
- It refers to a group of disorders characterised by clonal proliferation of haematopoietic cells, including erythroid, myeloid and megakaryocytic forms. The syndrome is characetrised by ineffective haemopoiesis due to increased susceptibility of clonal myeloid progenitors to apoptosis, which leads to cytopenias despite a generally hypercellular marrow.
- Progression to acute myeloid leukaemia occurs in a third of patients. This results from a shift from apoptosis to proliferation of clonal progenitors.
- Diagnosis requires demonstration of cytologic dysplasia in one or more of the different bone marrow cell lines in patients with persistent or progressive cytopenia or demonstration of increased myeloblasts (5–19%).

Aetiology

- The cause of MDS is unknown; however, exposure to radiation, certain pesticides, and some chemotherapeutic (particularly alkylating agents and topoisomerase inhibitors) and non-chemotherapeutic agents may induce MDS.
- Another factor is aging. The median age of patients with MDS is 65 years.

Classification

- The disease can be classified by the WHO criteria given in 2008. Most physicians do not follow the old FAB Classification.

WHO Classification (2008)

Subtype	Peripheral blood	Bone marrow
• Refractory cytopenias with unilineage dysplasia (RCUD):		
• Refractory anaemia (RA)	Anaemia <1% blasts	Unilineage erythroid dysplasia in ≥10% of cells <1% blasts
• Refractory neutropenia (RN)	Neutropenia <1% blasts	Unilineage granulocytic dysplasia in ≥10% of cells <5% blasts
• Refractory thrombocytopenia (RT)	Thrombocytopenia <1% blasts	Unilineage megakaryocytic dysplasia in ≥10% of cells <5% blasts

Subtype	Peripheral blood	Bone marrow
• Refractory anaemia with ring sideroblasts (RARS)	Anaemia No blasts	Unilineage erythroid dysplasia ≥15% of erythroid precursors are ring sideroblasts <5% blasts
• Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenia(s) <1% blasts No Auer rods	Multilineage dysplasia ± ring sideroblasts <5% blasts No Auer rods
• Refractory anaemia with excess blasts-1 (RAEB-1)	Cytopenia(s) <5% blasts No Auer rods	Unilineage/multilineage dysplasia 5–9% blasts No Auer rods
• Refractory cytopenia with multilineage dysplasia and ring sideroblasts (RCMD-RS)	Cytopenias (bi- or pancytopenia) <1% blasts No Auer rods	Multilineage dysplasia ≥15% of erythroid precursors are ring sideroblasts <5% blasts
• Refractory anaemia with excess blasts-2 (RAEB-2)	Cytopenia(s) 5–19% blasts Auer rods ±	Unilineage/multilineage dysplasia 10–19% blasts Auer rods ±
• MDS associated with isolated del(5q) [Del(5q)]	Anaemia Normal or high platelets	Isolated 5q31 chromosome deletion Anaemia, hypolobated megakaryocytes
• MDS, unclassifiable (MD-U)	<1% blasts Cytopenia(s) Blasts <1%	<5% blasts Does not fit other categories Dysplasia and <5% blasts

Clinical Features

- The most significant features are due to failure of bone marrow to produce normal blood cells. Hence, most patients develop anaemia, leucopenia and thrombocytopenia.
- Extramedullary haematopoiesis may occur leading to hepatomegaly and splenomegaly but is uncommon.

Diagnosis

- The minimal morphologic criterion for the diagnosis of an MDS is dysplasia in at least 10% of cells of any one of the myeloid lineages.
- A complete blood count may give clues to this diagnosis:
  - Anaemia is the most common feature, usually associated with macrocytosis and anisocytosis. Some degree of thrombocytopenia is usual. The platelets vary in size and some appear hypogranular.
  - The WBC count may be normal, increased or decreased. Neutrophils also show variation in size. Morphologic abnormalities are often observed in the granulocytes. These can include bilobed or unsegmented nuclei (pseudo-Pelger–Huet abnormality) or hypersegmented nuclei. Granulation abnormalities vary from an absence of granules to abnormal distribution inside the cytoplasm (Dohle bodies).
  - Immature myeloid cells are present in less well-differentiated.
- The bone marrow aspirate is hypercellular or normal in initial stages. It shows dysplastic features in one or several myeloid series. Myelofibrosis is occasionally present at diagnosis or may develop during the course of MDS. Bone marrow biopsy is useful when marrow is hypocellular as it helps in detecting fibrosis and also helps in differentiating it from aplastic anaemia or acute myeloid leukaemia.
- Cytogenetic study of the marrow is the most important test for establishing the diagnosis.
- In patients with megaloblastic features on bone marrow, serum vitamin B_{12} and folate levels should be measured.

Treatment

- Therapy is supportive with packed cell transfusions for anaemia, platelet transfusions for bleeding associated with thrombocytopenia and antibiotic therapy for infections. Iron chelators are required to reduce iron overload from multiple transfusions.
- In some patients, EPO and G-CSF may be useful to ameliorate symptoms but survival benefit has not been shown.
- Other options including use of thalidomide, lenalidomide (a derivative of thalidomide), 5-azacytidine and decitabine. 5-azacytidine and decitabine (hypomethylating agents) have been shown to decrease blood transfusion requirements and to retard the progression of MDS to AML. Lenalidomide is beneficial in the 5q- syndrome.
- Allogenic haematopoietic stem cell transplantation is the only potentially curative approach to MDS. However, it may be offered to less than 5–10% of patients because MDS is most commonly diagnosed in patients in their seventh or eighth decade of life.

Q. Discuss the types, clinical features, investigations, clinical staging and management of chronic lymphocytic leukaemia.

Definition

- Chronic lymphocytic leukaemia (CLL) is characterised by excessive accumulation of mature-appearing lymphocytes in the peripheral blood, associated with infiltration of the bone marrow, spleen and lymph nodes.

Types

- More than 95% of the cases of CLL are due to the expansion of B lymphocytes. These express B-cell antigens (CD19, CD20 and CD24) and CD5, which is typically found on T cells.
- Less than 5% are due to the expansion of T lymphocytes.

Clinical Features

- Most common form of chronic leukaemia.
- Common in patients over 50 years; peak age around 65 years.
- More in males than in females (2:1).
- 25% of the patients are asymptomatic.
- Generalised lymphadenopathy and hepatosplenomegaly.
- Slowly developing anaemia (due to immune haemolysis and bone marrow infiltration).
- Recurrent infections due to hypogammaglobulinaemia. *Streptococcus pneumoniae*, *Staphylococcus* and *Haemophilus influenzae* cause most of the infections. Herpes zoster also frequent.
- Bleeding manifestations extremely uncommon.
- May transform to prolymphocytic leukaemia (prolymhocytes >55%) or a large-cell lymphoma (Richter's syndrome).

Investigations

- Mild to moderate anaemia.
- Total leucocyte count is raised to the range of 50,000–200,000/mm^3.
- Peripheral smear examination:
  - More than 95% of the cells are mature-appearing lymphocytes of the small variety.
  - Prolymphocytes may be present in varying proportions.
  - Platelets are normal or reduced in number (autoimmune thrombocytopenia).
- Bone marrow is hypercellular with infiltration of small and medium sized lymphocytes.
- Direct Coombs' test may be positive indicating an autoimmune haemolytic process.
- Lymph node biopsy shows well-differentiated, small, non-cleaved lymphocytes.
- Serum folic acid levels are low.

Diagnostic Criteria

- At least 5×10^9 lymphocytes/L (5000/mm^3)
- Duration of lymphocytosis >2 months
- Atypical/immature cells ≤55% of lymphoid cells
- Low density of surface Ig (IgM or IgD) with κ or λ light chains
- B-cell surface antigens (CD19, CD20, CD23)
- CD5 surface antigen

Clinical Staging

Binet Staging

Stage	Features	Survival
A	No anaemia or thrombocytopenia Less than 3 areas of lymphoid enlargement	>10 years
B	No anaemia or thrombocytopenia 3 or more areas of lymphoid enlargement	7 years
C	Anaemia (<10 g/dL) and/or thrombocytopenia (<100,000/mm^3) present, regardless of the number of areas of lymphoid enlargement	2 years

Lymphoid enlargement includes cervical, axillary and inguinal lymph nodes, and liver and spleen enlargement.

Revised Rai Staging

Risk	Features	Survival
Low	Absolute lymphocytosis (>5,000/mm^3) without adenopathy, hepatosplenomegaly, anaemia or thrombocytopenia	>10 years
Intermediate	Absolute lymphocytosis with lymphadenopathy with or without hepatosplenomegaly, without anaemia or thrombocytopenia	7 years
High	Absolute lymphocytosis and anaemia (haemoglobin <11 g/dL) or thrombocytopenia (<100,000/mm^3) with or without lymphadenopathy, hepatomegaly or splenomegaly	1.5–3 years

Treatment

- Therapy is indicated when any of the following features is present:
    - (i) Fever without evidence of infection, extreme fatigue, night sweats, weight loss.
    - (ii) Increasing anaemia or thrombocytopenia due to bone marrow failure.
    - (iii) Bulky or progressive lymphadenopathy; massive or progressive splenomegaly.
    - (iv) Autoimmune cytopenias not responsive to corticosteroids.
    - (v) Rapidly rising lymphocyte count in peripheral blood (doubling time <6 months).
- Based on revised Rai (or Binet staging), treatment options are given in the box.

- Low risk (or Stage A)	No specific treatment, but only reassurance

- Intermediate risk (or Stage B)	Asymtomatic:
	  - No specific treatment
	  - Symptomatic, medically fit:
	  - Fludarabine + chlorambucil + rituximab

	- Bendamustine + rituximab
	- Fludarabine + rituximab
	Symptomatic, medically unfit:
	- Chlorambucil
	- Bendamustine
	Local radiotherapy to troublesome lymph nodes
• High risk (or Stage C)	As for symptomatic intermediate risk (or Stage B)
	Alemtuzumab + stem cell transplantation
	Combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) in refractory cases
	Packed cell transfusion for anaemia
	Prednisolone for haemolytic anaemia and thrombocytopenia
	Splenectomy for symptomatic splenomegaly

Chlorambucil (Leukeran)

- Two regimens are recommended in CLL:
  - Continuous low dose therapy—5 mg daily orally.
  - Intermittent high dose therapy (pulse therapy)—0.4 mg/kg every 2 weeks.
- Increased incidence of myelodysplasia and acute myeloid leukaemia.
- Other alkylating agent used in CLL is bendamustine

Purine Analogues:

- Three purine analogues are currently used in CLL: fludarabine, cladribine and pentostatin. Fludarabine is the best studied agent of the three in CLL.
- Fludarabine
  - Dose—25–30 mg/m^2 intravenously daily for 5 days every 4 weeks.
  - Potential complications—autoimmune haemolytic anaemia; opportunistic infections including *Legionella pneumophila*, *Pneumocystis jeroveci*, *Listeria monocytogenes* and cytomegalovirus.

Rituximab and Alemtuzumab

- Are monoclonal antibodies against CD20 and CD52, respectively.
- CD20 present on normal and malignant B cells.
- CD52 present on all CLL cells.
- Side effects include fever, chills, myalgias, nausea, and headache.

Q. Discuss the clinical features, investigations and management of hairy cell leukaemia.

Clinical Features

- Hairy cell leukaemia is a malignant expansion of B lymphocytes.
- Common in patients over 40 years with 4:1 male/female predominance.
- Symptoms are due to massive splenomegaly, pancytopenia and vasculitis (erythema nodosum and cutaneous nodules). Lymphadenopathy is rare.
- Hip pain due to bone lesions.
- Infections appear to be the most common cause of death.
- An increased risk of secondary malignancies, particularly Hodgkin's lymphoma, non-Hodgkin's lymphoma and thyroid cancer.

Investigations

- Total leucocyte count is normal or low. Pancytopenia, particularly monocytopenia occurs in several patients.
- Peripheral smear shows the characteristic hairy cells. These are the malignant B lymphocytes. The hairy structures on the surface of the cell are cytoplasmic projections. They have an eccentrically placed nucleus and foamy cytoplasm. These hairy cells stain positively for tartrate-resistant acid phosphatase (TRAP).

- Bone marrow is difficult to be aspirated ("dry tap") and biopsy shows fibrosis with infiltration by mononuclear cells and hairy cells.
- Splenic histology reveals mononuclear cell infiltration of red pulp and engorgement of sinuses.
- Liver biopsy reveals infiltration of portal triads by hairy cells.
- LAP score is very high.

Treatment

- Follows an indolent course. The current recommendation is to initiate treatment if patient develops cytopenia, symptomatic splenomegaly or constitutional symptoms (e.g. fever, night sweats and fatigue).
- Treatment of infections with antibiotics.
- Treatment of choice is chemotherapy with cladribine.
- α-interferon is not recommended as first-line agent as it is less effective.
- Pentostatin is another drug that is highly effective.
- Corticosteroids and myelotoxic drugs are contraindicated in hairy cell leukaemia.

Q. How do you classify splenomegaly? Enumerate the common causes of splenomegaly.

Classification and Causes

Mild splenomegaly (up to 5 cm)	
• Acute infections	Enteric fever, infectious hepatitis, infectious mononucleosis, brucellosis, septicaemia, cytomegalovirus, toxoplasmosis
• Subacute and chronic infections	Tuberculosis, infective endocarditis, syphilis, brucellosis, chronic bacteraemia, HIV
• Parasitic infestations	Malaria, kala-azar
Moderate splenomegaly (up to umbilicus)	Lymphomas, portal hypertension, acute leukaemias, chronic lymphocytic leukaemia, chronic myeloid leukaemia, chronic haemolytic anaemias, malaria, kala-azar, sarcoidosis
Massive splenomegaly (below umbilicus)	Chronic myeloid leukaemia, kala-azar, myelofibrosis, hairy cell leukaemia, tropical splenomegaly, kala-azar, portal hypertension, (extrahepatic portal vein thrombosis), Gaucher's disease, thalassaemia major, lymphomas, cysts and tumours of spleen

Q. Enumerate the common causes of massive splenomegaly. Discuss the differential diagnosis.

Common causes	Uncommon causes
• Chronic myeloid leukaemia	• Lymphomas
• Myelofibrosis	• Gaucher's disease
• Hairy cell leukaemia	• Thalassaemia major
• Tropical splenomegaly	• Cysts and tumours of spleen
• Kala-azar	
• Extrahepatic portal vein thrombosis	

Differential Diagnosis (also see individual conditions)

Chronic Myeloid Leukaemia

Clinical Features

- Peak age around 55 years.
- Symptoms of anaemia.
- Symptoms due to massive splenomegaly.

- Symptoms of hypermetabolic state.
- Occasional bleeding tendencies.
- Moderate to massive splenomegaly and hepatomegaly.
- Mild anaemia.

Investigations

- Normocytic normochromic anaemia.
- Total leucocyte count is markedly raised, always more than 20,000/mm³.
- Platelet count is usually increased.
- Peripheral smear shows full range of granulocyte precursors ranging from myeloblasts to myelocytes to metamyelocytes to mature neutrophils. The mature forms predominate. Myeloblasts are less than 5–10%. Nucleated red blood cells may be seen.
- Philadelphia chromosome is positive in more than 95% of cases.
- LAP score is very low.
- Vitamin B$_{12}$ levels are markedly elevated.

Myelofibrosis

Clinical features

- May remains asymptomatic for many years.
- Symptoms resulting from anaemia, massive splenomegaly and hypermetabolic state.
- Massive splenomegaly and hepatomegaly.

Investigations

- Markedly reduced haemoglobin in the late stages.
- Total leucocyte count may be normal, reduced or increased. Usually, it is raised in the early stages to the range of 10,000–20,000/mm³. Total leucocyte count is reduced in the late stages.
- Platelet count is raised in the early stages but reduced later.
- Peripheral smear examination:
  - Leucoerythroblastic blood picture.
  - Teardrop cells.
  - Anisopoikilocytosis.
  - Numerous nucleated red blood cells.
- Bone marrow study:
  - Usually a dry tap.
  - Increase in all three cells lines, hypercellularity and minimal fibrosis in early stages.
  - Decrease in all three cell lines, hypocellularity and dense fibrosis in late stages.
- Philadelphia chromosome is negative.
- LAP score is high.
- Increase in bone density of vertebrae and proximal ends of long bones.

Hairy Cell Leukaemia

Clinical Features

- May remain asymptomatic for years.
- Symptoms resulting from massive splenomegaly, infections and vasculitis.
- Hip pain due to bone lesions.
- Massive splenomegaly and hepatomegaly.

Investigations

- Total leucocyte count is normal or low.
- Peripheral smear shows the characteristic "hairy cells" that stain positively for TRAP.
- Bone marrow shows numerous mononuclear cells and hairy cells.
- Splenic histology shows mononuclear cell infiltration of red pulp and engorgement of sinuses.
- Liver biopsy reveals infiltration of portal triads by hairy cells.
- LAP score is very high.

Tropical Splenomegaly Syndrome (TSS)

- Better termed as hyperreactive malarial syndrome (HMS).
- Due to abnormal immune response to repeated malarial infections.

Clinical Features

- Patient is usually a resident of malaria endemic area.
- Low-grade fever may be occasionally present.
- Massive splenomegaly and hepatomegaly.
- Features of hypersplenism.

Criteria for Diagnosis

- Residence of malaria endemic area.
- Chronic splenomegaly, often massive.
- Serum IgM at least 2 standard deviations (SD) above the local mean.
- High malarial antibody titre.
- Hepatic sinusoidal lymphocytosis.
- Clinical and immunological response to antimalarial prophylaxis.

Investigations

- Malarial parasite is absent in peripheral blood smear.
- High levels of antimalarial antibodies in blood.
- IgM levels are markedly raised (up to 20 times).
- Light microscopic examination of liver shows sinusoidal lymphocytosis.
- Immunofluorescence microscopy of liver shows IgM aggregates in reticuloendothelial cells.

Kala-Azar (Visceral Leishmaniasis)

Clinical Features

- Patient is usually a resident of kala-azar endemic area.
- Fever with two peaks in 24 hours (camel hump fever) occurs in 10–15% cases.
- Massive splenomegaly and hepatomegaly.
- Generalised lymphadenopathy (in patients from Bengal) and pigmentation of face.

Investigations

- Anaemia, granulocytopenia and thrombocytopenia.
- Low serum albumin and high serum globulin, especially IgG.
- Leishmanian antibodies in blood.
- Leishmanin skin test.
- Demonstration of amastigotes (LD bodies) in aspirates of bone marrow, liver, spleen or lymph nodes.
- Culture of the aspirate for the organism.

Extrahepatic Portal Hypertension

Clinical Features

- Relatively earlier age at presentation.
- Episodes of haematemesis and/or melaena, not accompanied by hepatic decompensation.
- Absence of jaundice, ascites and other signs of chronic liver cell disease.
- Normal size of liver.
- Moderate to massive splenomegaly and signs of portal hypertension.

Investigations

- Normal liver function tests, prothrombin time and liver biopsy.
- Ultrasonography of abdomen shows normal hepatobiliary system and evidences of portal hypertension.
- Upper gastrointestinal scopy and barium swallow reveal varices.
- Splenoportovenogram (SPV) can delineate the collaterals and feeders.

Gaucher's Disease

- Autosomal recessive, lysosomal storage disorder.
- Deficiency of the enzyme acid β-glucocerebrosidase results in the storage of glucosylceramide within lysosomes of the monocyte-macrophage system.
- Three forms of the disease exist:
  - Infantile form.
  - Juvenile form.
  - Adult form (type 1).
- Clinical manifestations of the adult form include massive splenomegaly, cytopenias, skeletal dysplasias, bone pain, pathological fractures, vertebral collapse and aseptic necrosis of femoral head.
- Investigations:
  - Increase in serum acid phosphatase.
  - Characteristic foam cells in the peripheral smear.
  - Characteristic "Gaucher cells" in the bone marrow.
  - Enzyme assay establishes the diagnosis.
- Treatment:
  - Majority does not require any treatment.
  - Partial or total splenectomy in selected cases.
  - Enzyme replacement is currently the treatment of choice in significantly affected patients. Imiglucerase, a recombinant DNA-produced analogue of human β-glucocerebrosidase has proved highly efficacious in reducing hepatosplenomegaly and improving bone marrow involvement and haematological findings. Other recombinant glucocerebrosidase enzyme replacements include velaglucerase alpha and taliglucerase alfa. Recently, an oral preparation, eliglustat has been approved for use in adults with type 1 disease.

Differential Diagnosis

Table I

Differentiating feature	Chronic myeloid leukaemia	Myelofibrosis	Hairy cell leukaemia
Total count	Markedly raised to >20,000/µL	Raised to 10,000–20,000/µL	Normal or low
Differential count	Neutrophils >95%	Normal	Neutropenia and lymphocytosis
Peripheral smear	Full range of granulocyte precursors with mature forms predominating Myeloblasts <5–10% Few nucleated red blood cells	Leucoerythroblastic blood picture Tear drop cells Anisopoikilocytosis Numerous nucleated red blood cells	"Hairy cells" that stain positively for tartrate-resistant acid phosphatase (TRAP)
Bone marrow	Hypercellular Cells mainly of myeloid series, myelocytes being the predominant cells	Hypercellularity with increase in all three cell lines in early stages Hypocellularity with decrease in all three cell lines in late stages	Numerous mononuclear cells and "hairy cells" with fibrosis
Marrow fibrosis	Uncommon and minimal	Common and marked	Increase in marrow reticulin
LAP score	Markedly lowered	Raised	Markedly raised
Ph. chromosome	Positive	Negative	Negative
Vitamin B_{12} levels	Markedly raised	Raised	Normal

Table II

Differentiating feature	Tropical splenomegaly syndrome	Kala-azar	Extrahepatic portal hypertension
• Endemicity	Endemic	Endemic	Non-endemic
• Fever	Low grade	"Camel hump"	Absent
• GI bleeding	Absent	Absent	Present
• Immunoglobulins	IgM increased	IgG increased	—
• Antibodies	Antimalarial antibodies	Antileishmania antibodies	—
• Bone marrow	Malarial parasites (rare)	LD bodies	Normal
• Liver biopsy	Light microscopy shows sinusoidal lymphocytosis Immunofluorescence microscopy shows IgM aggregates in reticulo-endothelial cells	LD bodies, which are also seen in bone marrow, spleen and lymph nodes	Normal
• Evidences of portal hypertension on endoscopy, barium swallow and SPV*	Absent	Absent	Present

* SPV—Spleno-porto-venography

Q. Enumerate the causes, clinical features and treatment of hypersplenism.

- This is a term used to indicate anaemia, leucopenia and thrombocytopenia associated with prominent splenomegaly (due to any cause) and a normal or hypercellular bone marrow.
- No direct relation between splenic size and hypersplenism; however hypersplenism is more common among those who have gross splenomegaly.
  - Leucopenia and thrombocytopenia result from excessive sequestration of these cells in the large spleen.
  - Anaemia is believed to be dilutional, resulting from an increase in total plasma volume.

Common Causes

• Primary hypersplenism	No detectable cause
• Secondary hypersplenism	Portal hypertension, malaria, kala-azar, tropical splenomegaly syndrome, myeloproliferative disorders, tuberculosis

Clinical Features

- Symptoms related to the enlarged spleen such as abdominal fullness associated with feeling of heaviness and discomfort and pain in the left upper quadrant of the abdomen.
- Haematological symptoms: Symptoms related to thrombocytopenia, anaemia and leucopenia
- Symptoms and signs of the underlying diseases.

Treatment

- Primary hypersplenism is treated by splenectomy or partial splenic embolisation.
- Secondary hypersplenism is managed by tackling the underlying cause.

Q. What are lymphomas? What are the common types of lymphomas?

- Lymphomas are a heterogeneous group of neoplasms arising from lymphoid cells and almost always present as solid tumours. Majority of lymphoid cells are present in lymph nodes, spleen, bone marrow, thymus and gastrointestinal tract.

- The major types of lymphomas are Hodgkin's lymphoma or disease and non-Hodgkin's lymphoma. An uncommon lymphoma is mycosis fungoides.

Q. Discuss the pathological classification, clinical features, clinical staging, investigations and treatment of Hodgkin's lymphoma.

Q. Give a brief account of Read–Sternberg (RS) cell.

- Hodgkin's lymphoma (HL) is of B cell origin.
- Bimodal age incidence with one peak in young adults (15–35 years) and the other in older adults (45–75 years).
- Infection by HIV is a risk factor for developing Hodgkin's lymphoma where mixed cellularity and lymphocyte-depleted Hodgkin's lymphoma are common. Although the histologic features of Hodgkin's lymphoma are similar in HIV/AIDS and immunocompetent individuals, there are several clinical differences. Patients with HIV/AIDS have advanced stage disease at the time of diagnosis, an aggressive clinical course, poor response to conventional therapy, non-contiguous spread, frequent involvement of bone marrow and other extranodal sites, and a strong association with EBV (80%–100%).
- Association with Epstein–Barr virus demonstrated in 30–50% immunocompetent patients also.

Pathological Classification

- WHO (2008) has divided Hodgkin's lymphoma into two types. Prognosis varies depending upon the histological type.
  - Classic HL is characterised by presence of Reed-Sternberg cells in an inflammatory background.
  - Nodular lymphocyte predominant HL lacks Reed–Sternberg cells but is characterised by the presence of lymphocyte-predominant cells, sometimes termed as popcorn cells.

WHO Classification of Hodgkin's Lymphoma

- Nodular lymphocyte predominant Hodgkin's lymphoma (<5%)
- Classic Hodgkin's lymphoma (>95%)
  - Nodular sclerosis classic Hodgkin's lymphoma
  - Mixed cellularity classic Hodgkin's lymphoma (most common type in India)
  - Lymphocyte-rich classic Hodgkin's lymphoma
  - Lymphocyte-depleted classic Hodgkin's lymphoma

Clinical Manifestations

- Starts in one lymph node group (unifocal origin) and spreads in a predictable manner to the adjacent lymph node group (contiguous spread).
- The disease usually begins as painless enlargement of one group of cervical lymph nodes. Less commonly, the disease may start in the mediastinal or axillary nodes, and rarely in the abdominal, pelvic or inguinal nodes. The involved nodes are discrete, non-tender and "rubbery" in consistency. Alcohol-induced discomfort in the lymph nodes is a common feature of Hodgkin's lymphoma. Sites that are rarely involved by Hodgkin's lymphoma include Waldeyer's ring, and mesenteric, epitrochlear and popliteal nodes.
- Compression of various organs by lymph node masses or infiltration of various organs can produce clinical effects like dysphagia, dyspnoea, Horner's syndrome, hoarseness of voice, superior vena cava syndrome, inferior vena cava obstruction, jaundice and paraplegia. Mediastinal involvement is seen in 80% cases of nodular sclerosis classic Hodgkin's lymphoma, of which more than half have bulky mediastinal disease.
- Splenomegaly is uncommon in the beginning, but as the disease advances, hepatosplenomegaly becomes prominent.
- Involvement of extralymphatic organs is a late feature in Hodgkin's lymphoma.
- The "B" symptoms or systemic symptoms that place the patient in the "B" category are the following:
  - Unexplained weight loss of more than 10% of the body weight in the previous 6 months.
  - Unexplained fever above 38°C during the previous month.
  - Heavy night sweats during the previous month.
- The classical Pel–Ebstein fever is rarely seen. This fever occurs in a cyclical pattern, characterised by several days or weeks of fever alternating with afebrile periods.
- Pruritus is a common symptom, and is troublesome at times.
- Nephrotic syndrome may occur from immune complex deposition in the kidneys.

- Hodgkin's lymphoma is associated with depressed cell-mediated immunity resulting in a higher risk of infections like herpes zoster, tuberculosis, cryptococcal infections, cytomegalovirus infections and infection with candida species.

Clinical Staging (Ann Arbor classification)

- Lymphatic structures are defined as lymph nodes, spleen, thymus, Waldeyer's rings, appendix and Peyer's patches; liver and bone marrow are excluded.
- Each stage is further divided into A or B based on the absence or presence of systemic symptoms (B symptoms), respectively.

• **Stage I**	Involvement of a single lymph node region (I) or extralymphatic site (IE)
• **Stage II**	Involvement of two or more lymph node regions (II) or an extralymphatic site and lymph node regions on the same side (above or below) the diaphragm (IIE)
• **Stage III**	Involvement of lymph node regions on both sides of the diaphragm with (IIIE) or without (III) localised extralymphatic involvement or involvement of the spleen (IIIS) or both (IIISE)
• **Stage IV**	Diffuse involvement of one or more extralymphatic tissues (e.g., liver, bone marrow, pleura, lung, bone) with or without associated lymph node involvement.

Investigations

- Haemogram:
  - Normocytic normochromic anaemia is common. In advanced disease, microcytic anaemia usually develops due to defective iron utilisation.
  - Total leucocyte count may be normal, but is sometimes considerably raised with neutrophil leucocytosis.
  - Eosinophilia is present in about 20% of patients and thrombocytosis is seen in some cases.
  - In the terminal stages, there may be leucopenia and thrombocytopenia.
- Elevated serum alkaline phosphatase levels usually indicate bone marrow or liver involvement.
- Tissue biopsy, usually a lymph node biopsy, will establish the diagnosis. A fine needle aspiration is not recommended for diagnosis. Liver biopsy may provide the diagnosis in those with hepatomegaly.
- It is important to establish the extent of the disease. The investigations required for clinical staging include chest radiographs, liver function tests, renal function tests, abdominal ultrasound, bone marrow trephine and aspirate, and CT scan (neck, chest, abdomen and pelvis). Bone marrow biopsy is required only in presence of 'B' symptoms, clinically advanced disease or infra-diaphragmatic disease and in those with bone lesions, bone pain, hypercalcaemia, or an elevated serum alkaline phosphatase.
- PET scan is sensitive for evaluating the extent of disease and is an integral part of initial staging. The sensitivity of [18]FDG-PET and PET/CT is higher than that of CT in order to identify both nodal and extranodal disease. It is also very useful at the completion of therapy to document remission.

Reed–Sternberg (RS) cell

- The Reed–Sternberg (RS) cells are pathognomonic of Hodgkin's lymphoma. The presence of RS cells in histology specimen differentiates Hodgkin's lymphoma from non-Hodgkin's lymphoma. These cells are derived from lymphocytes (hence the name Hodgkin's disease was changed to Hodgkin's lymphoma)
- RS cells are presumed to evolve either due to viral infection or underlying immune derangement
- They are giant cells with paired, mirror imaged nuclei (binucleate) with large nucleoli in each nucleus ("owl's eye" cells)
- On immunophenotyping, these cells are usually CD15+ and CD30+. Nearly 40% are also CD20+.
- In contrast to non-Hodgkin's lymphomas (NHL) and other malignant tumours that are composed almost exclusively of malignant cells, RS cells comprise less than 1% of cells in the affected tissues
- Uninucleate cells with cytologic features identical to those of RS cells are referred to as Hodgkin's cells. Hodgkin's cells by themselves are insufficient for a definitive diagnosis on the initial biopsy, but are sufficient to establish a diagnosis of relapsed disease when the immunophenotype of these Hodgkin's cells is characteristic

Unfavourable Features for Stage I and II Hodgkin's Lymphoma

- Large mediastinal adenopathy (at least 33% as wide as the chest)
- Any single node or nodal mass that is 10 cm or greater in diameter.
- B symptoms
- >3 sites of involvement
- Erythrocyte sedimentation rate >50

Management

Radiotherapy

- Megavoltage radiotherapy to a dose of 3500–4000 cGy is given to the involved sites over a period of 4 weeks (involved-field radiotherapy).
- Radiotherapy given to an extended area that includes all lymph node-bearing areas above diaphragm is known as mantle field radiation. Sometimes periaortic lymph nodes and spleen (spade field) are also included.
- Inverted Y field radiotherapy includes periaortic iliac, hypogastric and inguinal lymph nodes, and spleen.
- Indications for radiotherapy are the following:
  - Stage I disease.
  - Stage II disease without any unfavourable features.
  - After chemotherapy to sites where there was originally bulk disease.
  - To lesions causing serious pressure problems.
- Stages I and II A disease can be treated with radiotherapy given to an extended area that includes all lymph node-bearing areas above diaphragm (mantle field), and sometimes including the periaortic lymph nodes and spleen (spade field).
- In stages II B and III A, standard chemotherapy with or without radiotherapy is given. In such case, radiotherapy involves mantle field as well as inverted Y field (periaortic iliac, hypogastric and inguinal lymph nodes, and spleen).

Chemotherapy

- Combination chemotherapy has been shown to be highly effective. The regimens commonly used are given in the box.
- These regimens are given on a 28-day cycle (21-day cycle for BEACOPP escalated for advanced disease) for a minimum of 2 pulses and up to 9, if necessary. Cure rates >75% can be achieved.

•	ABVD	Doxorubicin (adriamycin), bleomycin, vinblastine, dacarbazine
•	Stanford V	Doxorubicin, mechlorethamine (nitrogen mustard), vincristine, vinblastine, bleomycin, etoposide, prednisone
•	BEACOPP escalated	Bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone in escalated dose

Recommendations on Treatment

Stage IA and IIA Classic HL (without unfavourable features)

- Chemotherapy (ABVD for two to four cycles over 8-16 weeks or Stanford V for two cylces over 8 weeks) followed by involved-field radiotherapy is the standard of treatment.
- Restaging is done at the completion of treatment.
- Cure rates (free of disease at 5 years) of about 80-90% can be achieved with this therapy.

Stage I and II Classic HL (with unfavourable features)

- Two cylces of ABVD are given initially followed by restaging. If a complete response occurs, 2 to 4 additional cycles are administered followed by involved-field radiotherapy.
- For Stanford V, three cycles are given followed by restaging and if complete or partial response occurs, involved-field radiotherapy is given.

Stage III and IV Classic HL

- Chemotherapy (ABVD, Stanford V or BEACOPP escalated) along with radiotherapy to initially bulky lymph nodes (>5 cm).
- Overall survival is 75-90% at five years.

Nodular Lymphocyte Predominant HL

- Involved-field radiotherapy for stage IA or IIA disease
- Chemotherapy (with or without radiotherapy) or rituximab either as a single agent or in combination with chemotherapy (with or without radiotherapy) for stage IB, IIB, III and IV disease.

Bone Marrow Transplantation

- Autologous haematopoietic bone marrow transplantation successful in nearly 40% cases even after the failure of chemotherapy.

Late Complications

- Occur due to high cure rates achieved with treatment.
- Second malignancies including acute leukaemia and solid organ cancers. Acute leukaemia generally occurs within 10 years of use of alkylating agents in combination with radiotherapy. Risk is greater with MOPP as compared to ABVD. Solid organ cancers usually occur more than 10 years after treatment and are associated with use of radiotherapy.
- Cardiac failure and accelerated coronary artery disease due to radiotherapy and use of doxorubicin.
- Pulmonary fibrosis (if bleomycin or radiation is used).
- Hypothyroidism.

Q. Discuss the pathological classification, clinical staging, clinical features, investigations and management of non-Hodgkin's lymphoma.

- In non-Hodgkin's lymphoma, there is a malignant monoclonal proliferation of lymphoid cells, the majority of cases (~80%) originating in B cell, a minority in T cell (15–20%) and rarely in natural-killer cells.
- Non-Hodgkin's lymphomas merge with lymphoblastic and lymphocytic leukaemias.

Aetiology

- Unknown in most cases.
- Associated with chronic inflammatory or autoimmune diseases such as Sjogren syndrome, Hashimoto's thyroiditis and rheumatoid arthritis.
- Associated with chronic infection (e.g. association between mucosa-associated lymphoid tissue lymphomas and *Helicobacter pylori* infection).
- Immune suppression as seen with solid organ transplantation and HIV infection.

Pathology and Classification

- International Working Formulation was drawn up in 1982 from the Rappaport and the Kiel classifications and is given in the box.

• **Indolent or low-grade**	Small lymphocytic Follicular, predominantly small cleaved cells
• **Aggressive or intermediate-grade**	Follicular, mixed, small cleaved and large cleaved cells Follicular, predominantly large cell, cleaved and/or non-cleaved
• **Highly aggressive or high-grade**	Diffuse, small cleaved cell Diffuse, mixed, large and small cell Diffuse, large cell, cleaved or non-cleaved Large cell, immunoblastic (B- or T-cell type) Lymphoblastic Small non-cleaved cell (Burkitt's and non-Burkitt's)

- The size of the lymphoid cells is a guide to prognosis. Small-cell disease (mature lymphocytes) is associated with low-grade and large-cell disease (immature lymphoid cells) with high-grade disease.
- Most follicular lymphomas are low-grade with good prognosis, and most diffuse lymphomas are high-grade with poor prognosis.

- A WHO classification was introduced in 2008 to cover all types of lymphoid malignancies. It subdivides tumours into those of B-cell versus T/NK-cell origin and those with an immature or blastic appearance versus those developing from more mature stages of lymphoid development. A lymphoma that originates in the lymphatic tissue in the marrow is designated as lymphocytic leukaemia or lymphoblastic leukaemia. CLL now belongs to the NHL group together with its non-leukaemic counterpart, and small lymphocytic lymphoma. Plasma cell malignancies are also recognised as NHL subtypes according to WHO. Classification requires performance of immunophenotyping and might require cytogenetics, fluorescent in situ hybridisation (FISH) and antigen receptor gene rearrangement studies.

WHO Classification of Lymphoid Malignancies (important categories)

B cell	T-cell and NK-cell
Precursor B-cell neoplasm	**Precursor T-cell neoplasm**
• Precursor B-cell acute lymphoblastic leukaemia	• Precursor T-cell acute lymphoblastic leukaemia
Mature (peripheral) B-cell neoplasms	**Mature (peripheral) T/NK-cell neoplasms**
• B-cell chronic lymphocytic leukaemia/small lymphocytic lymphoma	• T-cell prolymphocytic leukaemia
• B-cell prolymphocytic leukaemia	• T-cell granular lymphocytic leukaemia
• Lymphoplasmacytic lymphoma— Waldenstrom macroglobulinaemia	• Aggressive NK-cell leukaemia
• Splenic marginal zone B-cell lymphoma	• Adult T-cell lymphoma/leukaemia (HTLV1)
• Nodal marginal zone B-cell lymphoma	• Enteropathy-type T-cell lymphoma
• Hairy cell leukaemia	• Cutaneous T-cell lymphoma (Mycosis fungoides and Sezary syndrome)
• Plasma cell myeloma/plasmacytoma	• Anaplastic large cell lymphoma
• Mucosa-associated lymphoid tissue (MALT) lymphoma (Extranodal marginal zone B-cell lymphoma)	• T/null cell, primary cutaneous lymphoma
• Follicular lymphoma	• Angioimmunoblastic T-cell lymphoma
• Mantle cell lymphoma	• Anaplastic large cell lymphoma, T/null cell, primary systemic type
• Diffuse large B-cell lymphoma	
• Burkitt's lymphoma and leukaemia	
• Mediastinal (Thymic) large B-cell lymphoma	
• Primary CNS lymphoma	

- Precursor B-cell or T-cell acute lymphoblastic leukaemia
  - Clinically, a case is defined as lymphoma if there is a mass lesion in the mediastinum or elsewhere and <25 percent blasts in the bone marrow. It is classified as leukaemia if there are >25 percent bone marrow blasts, with or without a mass lesion.
- Follicular lymphoma and diffuse large B-cell lymphoma are the two most common types and together account for more than 50% of cases. In AIDS patients, diffuse large B-cell lymphoma, Burkitt lymphoma and primary central nervous system (CNS) lymphoma are most commonly seen non-Hodgkin's lymphomas.
- Non-Hodgkin's lymphoma may be classified as indolent and aggressive

Indolent	Aggressive
• Follicular lymphoma	• AIDS-associated lymphoma
• Cutaneous T-cell lymphoma (Mycosis fungoides and/ Sezary syndrome)	• Anaplastic large cell lymphoma
• Lymphoplasmacytic lymphoma	• Burkitt's lymphoma
• Mucosa associated lymphoid tissue (MALT) lymphoma	• Central nervous system lymphoma
	• Diffuse large B-cell lymphoma
• B-cell chronic lymphocytic leukaemia/small cell lymphocytic lymphoma	• Lymphoblastic lymphoma
	• Mantle cell lymphoma
• Nodal marginal zone B-cell lymphoma	• Precursor B-cell and T-cell lymphoma/ leukaemia

Clinical Features

- Can occur at any age, but the peak incidence is around 60 years.
- Multicentric in origin, and spreads rapidly to non-contiguous areas. The disease is usually widespread at the time of diagnosis.
- Discrete, painless, firm, lymph nodal enlargement is the most common presentation. Waldeyer's ring and epitrochlear lymph nodes are frequently involved.
- The "B" symptoms of fever, night sweats and weight loss are less prominent.
- Early involvement of extralymphatic organs is a feature of non-Hodgkin's lymphoma. Gastrointestinal tract (stomach), thyroid, skin, sinuses and central nervous system are frequently involved. Paraplegia can occur from compression of spinal cord by an extradural lymphoma. Other pressure effects are dysphagia, breathlessness, vomiting, intestinal obstruction, ascites and limb oedema.
- Patients with lymphoblastic lymphoma often present with an anterior mediastinal mass.
- Bone marrow involvement is common and early, and can produce cytopenias.
- Involvement of liver and spleen results in hepatosplenomegaly.
- Bone involvement may manifest as pathological fractures with pain.
- Burkitt's lymphoma typically disseminates to the bone marrow and meninges and involves extranodal sites.

Clinical Staging (Ann Arbor classification)

- Ann Arbor classification may be used to define patients into limited (stage I and II) and advanced (stage III and IV) lymphomas. However, it is more useful in Hodgkin's lymphoma rather than in non-Hodgkin's lymphoma. Further, "B" symptoms are not included as they are not useful in predicting prognosis.

Investigations

- Haemogram:
  - Moderate degrees of anaemia may be seen when there is significant marrow involvement.
  - Blood counts are usually normal, but some patients show lymphocytosis. A leukaemic phase develops in 20–40% of lymphocytic lymphomas and rarely in intermediate-grade lymphomas. High-grade lymphomas may frequently be leukaemic.
  - Splenomegaly with hypersplenism or a complicating autoimmune haemolytic anaemia can result in low haemoglobin levels, reticulocytosis and positive Coombs' test.
- Bone marrow aspiration and trephine biopsy should be done early, since marrow involvement is common.
- Other investigations required are immunophenotyping of blood, lymph node and marrow lymphoid cells and estimation of serum immunoglobulin levels. Immunohistochemical study is essential for differentiating various subtypes of NHL and also to determine prognosis as these will influence the choice of therapy. It can be performed by flow cytometry and/or immunohistochemistry for B-cell markers CD79A and CD20, T-cell marker CD3, and the proliferative marker Ki67. Ki67 fraction >40% is highly suggestive of a high-grade lymphoma.
- In addition, serum levels of LDH and β_2-microglobulin, and serum protein electrophoresis are often included in the evaluation as these affect the prognosis.
- A diagnostic spinal tap directly combined with a first prophylactic instillation of cytarabine and/or methotrexate is indicated in high-risk patients, especially with involvement of CNS, orbit, bone marrow, testis, spine or base of the skull. It is also indicated in the case of HIV-associated lymphoma and highly aggressive lymphoma.
- The investigations required for staging the disease are the same as that for Hodgkin's lymphoma.

Management

- Radiotherapy involves involved-field treatment which is given for localised disease.
- Chemotherapy can be given as a single drug therapy with chlorambucil or as a combination therapy with multiple drugs.
- In cases with high tumour load, special precautions (e.g. corticosteroid and alkaline diuresis) are required to avoid tumour lysis syndrome.
- Stem cell transplantation may be done if the disease relapses.

Diffuse large B cell lymphoma (DLBCL)

- Constitutes about 30–50% of all non-Hodgkin's lymphomas.
- AIDS-related diffuse large B-cell lymphoma is the most common AIDS-related non-Hodgkin's lymphoma.

- Patients of all ages with stage I-II DLBCL and no adverse prognostic factors (non-bulky disease, age <60 years, serum LDH normal, performance status 2–4, extranodal involvement ≤1 site) should receive 3–4 cycles of chemotherapy (R-CHOP i.e. rituximab plus cyclophosphamide, hydroxydaunorubicin or Adriamycin, oncovin or vincristine and prednisolone) plus involved-field radiotherapy, or 6–8 cycles of chemotherapy alone.
- All other patients should receive 6–8 cycles of chemotherapy (R-CHOP).

Follicular Lymphoma

- Slow growing
- Recurrence rate high after initial treatment
- For stage I and II, local radiotherapy alone or observation (if significant morbidity expected from radiotherapy).
- For stage III and IV:
  - If asymptomatic patient, observation without any specific therapy is often recommended.
  - For symptomatic patient, administer chemotherapy (R-CHOP or Bendamustine plus rituximab).

Q. How do you differentiate Hodgkin's lymphoma from non-Hodgkin's lymphoma?

Hodgkin's lymphoma	Non-Hodgkin's lymphoma
• Bimodal peak incidence, 15–35 years and 45–70 years	• Peak incidence around 60 years
• "B" symptoms are more common	• "B" symptoms are less common
• Alcohol-induced discomfort in lymph nodal region	• —
• Usually well localised at the time of diagnosis	• Usually widespread at the time of diagnosis
• Unifocal origin and contiguous spread	• Multicentric origin and non-contiguous spread
• Involvement of extralymphatic organs is late	• Involvement of extralymphatic organs is early
• Waldeyer's ring involvement is uncommon	• Waldeyer's ring involvement is common
• Epitrochlear node involvement is rare	• Epitrochlear node involvement is common
• Early involvement of para-aortic lymph nodes	• Early involvement of mesenteric lymph nodes
• Mediastinal involvement is common	• Mediastinal involvement is uncommon
• Bone marrow involvement is late	• Bone marrow involvement is early

Q. Describe Burkitt's lymphoma/leukaemia.

- It is a high-grade, B-cell, non-Hodgkin's lymphoma having small non-cleaved cells.
- Has the fastest doubling time among human tumours
- Often presents with extranodal involvement or as leukaemia.
- Three variants: endemic, sporadic and immunodeficiency-associated BL.
- Endemic form mainly seen in tropical Africa and New Guinea.
- Epstein–Barr (EB) virus plays an important aetiological role.
- Majority of the cases occur in children.
- Nearly 80% cases have a translocation of *c-myc* from chromosome 8 to the immunoglobulin (Ig) heavy chain region on chromosome 14 [t(8;14)].

Clinical Features

- Endemic form is most commonly seen in young children (4–7 years) with frequent involvement of jaw, periorbital area and kidneys. Some may develop sudden paraplegia.
- Sporadic form presents mainly with abdominal tumours. One-fourth has ileocaecal disease and present with either a right lower quadrant mass or pain from intussusception. Some cases are classified as Burkitt's leukaemia and are characterised by extensive marrow infiltration (more than 25% blasts), with possible bone pain as a presenting feature.

- Immunodeficiency form is associated with HIV infection and usually occurs with CD4 counts above $200/mm^3$. It again presents with abdominal involvement.
- Mandible and maxillary bone involvement leads to deformity, loosening of teeth and extrusion of the eye with loss of vision.
- Abdominal involvement presents as tumours due to bilateral involvement of kidneys, adrenals, ovaries, bowel and lymph nodes.
- Other sites of involvement are CNS, long bones, salivary glands, thyroid, testes, heart, breast and bone marrow. CNS involvement is common in adults.

Investigations

- Histological examination shows presence of a monotonous infiltrates of medium-sized blastic lymphoid cells that show round nuclei with clumped chromatin and multiple, centrally located nucleoli. These are of B-cell lineage (CD20+ and CD79a+). The rate of proliferation and rate of death (apoptosis) are high, with the dead cells being taken up by pale histiocytic cells within the tumour that punctuate the low-power view, giving a "starry sky" appearance.
- Chromosome analysis may show 8/14 or in some cases, 2/8 or 8/22 translocation.
- Antibodies to EB viral capsid antigen may be detected (in most patients with endemic type, and in several patients with sporadic and HIV-associated tumours).

Treatment

- Treatment must be initiated urgently with adequate hydration to prevent tumour lysis syndrome.
- High-intensity, brief-duration chemotherapy is highly effective. Regimens include CHOP (cyclophosphamide, hydroxy-doxorubicin or doxorubicin, vincristine, prednisolone) regimen or rituximab plus EPOCH (etoposide, prednisolone, vincristine, cyclophosphamide and hydroxydoxorubicin) or CODOX-M/IVAC regimen (cyclophosphamide, vincristine, doxorubicin, methotrexate/ifosfamide, etoposide or VP-16, cytarabine or Ara-C).
- Prophylactic intrathecal methotrexate and hydrocortisone for meningeal prophylaxis.
- Cure rates as high as 70–80%.

Q. Briefly discuss adult T-cell lymphoma/leukaemia.

- It is a type of non-Hodgkin's lymphoma that is caused by human T-cell lymphotropic virus-I (HTLV-I).
- Major routes of HTLV-1 transmission are mother-to-child infections via breast milk, blood transfusion or sexual contact.
- Latency period between infection and development of disease is long (10–30 years).
- Four major presentations: acute, lymphomatous, chronic and smoldering.
- Most patients have an acute, aggressive disease characterised by peripheral blood lymphocytosis, lymphadenopathy, hepatosplenomegaly, skin infiltration, hypercalcaemia, lytic bone lesions and elevated LDH levels in blood. In these patients, median survival is 6 months. Opportunistic infections are commonly seen. Peripheral smear usually reveals characteristic, pleomorphic abnormal CD4-positive cells with indented nuclei (called "flower" or "cloverleaf" cells). Bone marrow involvement is usually not prominent.
- About 20% patients have lymphomatous form associated with generalised lymphadenopathy without leukaemia and a median survival of approximately 1 year.
- The chronic subtype (15% of cases) may have a low level absolute lymphocytosis in the peripheral blood associated with an exfoliative skin rash and a median survival greater than 2 years.
- The smoldering subtype (5% of cases) has a normal peripheral blood lymphocyte count and a small number of circulating tumour cells and skin rashes. There is no lymphadenopathy, hepatosplenomegaly or hypercalcaemia. Median survival is more than 2 years, but less than 10 years.
- Treatment offered to acute and lymphomatous forms.
  - Treatment of hypercalcaemia and opportunistic infections.
  - Combination chemotherapy along with intrathecal drugs (methotrexate, cytarabine and hydrocortisone) may prolong life but usually does not produce remissions.
  - Combination antiretroviral drugs (zidovudine+interferon-α) may help some patients.

Q. Explain what is mucosa-associated lymphoid tissue (MALT) lymphoma or primary gastric lymphoma.

- It is a small-cell non-Hodgkin's lymphoma of B-cells that is extranodal in origin.
- Gastric type of MALT lymphoma is associated with *Helicobacter pylori* infection. Salivary gland MALT is associated with Sjogren's syndrome.
- Mainly seen in elderly patients with median age of 60 years.
- May occur in the stomach, orbit, intestine, lung, skin, soft tissue, bladder, kidney, salivary gland and CNS.
- May present as a mass or be associated with local symptoms such as upper abdominal discomfort, dyspepsia and rarely upper GI bleed in gastric MALT lymphoma.
- Localised to the organ from which it arises in about 40% cases and to the organ and surrounding lymph nodes in 30% cases. Bone marrow involvement is uncommon and occurs in only 15% cases. Distant metastasis can also occur.
- Endoscopic features of gastric MALT often mimic benign conditions like chronic gastritis or a peptic ulcer. Multiple biopsies are required for establishing diagnosis.
- Endoscopic ultrasound (EUS) useful for staging of gastric MALT lymphoma.
- Prognosis is good in most cases with 5-year survival of 75%.
- Low-grade gastric MALT lymphoma can be cured with antibiotic therapy aimed at the eradication of *H. pylori*.
- Localised MALT lymphomas can be treated with surgery, local radiotherapy, or rituximab.
- Extensive disease is treated with single agents like chlorambucil, cyclophosphamide, fludarabine or cladribine along with rituximab.

Q. Write a short note on mycosis fungoides and Sezary syndrome.

- These are rare forms of T-cell non-Hodgkin's lymphoma that have an insidious onset.
- Derived from CD4+ T cells of skin-associated lymphoid tissue.

Clinical Features

- Classic presentation of mycosis fungoides is occurrence of patches and plaques on non-sun exposed areas that may slowly evolve to tumours. The skin rash is usually itchy. Approximately 30% of patients present with skin tumours or erythroderma (erythrodermic mycosis fungoides) at disease onset.
- Sezary syndrome is an aggressive, leukaemic cutaneous T-cell lymphoma variant, characterised by a triad of circulating neoplastic T cells (Sezary cells), diffuse erythroderma and disabling pruritus, with/without associated lymphadenopathy. The circulating cells are malignant T cells with serpentine nuclei.
- Erythrodermic mycosis fungoides is differentiated from Sezary syndrome by absent/low circulating Sezary cell count and is regarded as a progression of mycosis fungoides, whereas Sezary syndrome typically arises de novo.

Treatment

- Local corticosteroid therapy most common therapy in early cases and is also used as an adjunct for other therapies. Topical nitrogen mustard and phototherapy have similar efficacy.
- Electron beam radiotherapy along with the application of nitrogen mustard or corticosteroids locally is a effective treatment in refractory/relapsed extensive plaque.
- Single-agent systemic therapy using immunomodulators such as interferons and retinoids often used if skin-directed therapy is inadequate or in cases of advanced disease.
- Chemotherapy (e.g. methotrexate, fludarabine) generally reserved for treatment refractory or rapidly progressive advanced cases.

Q. What are plasma cell disorders?

- Plasma cell disorders are monoclonal neoplasms developing from common progenitors in the B-lymphocyte lineage.
- These disorders are also known as monoclonal gammopathies, paraproteinaemias and plasma cell dyscrasias. These include the following diseases:
  - Multiple myeloma
  - Waldenstrom macroglobulinaemia

- Primary (AL) amyloidosis
- Solitary plasmacytoma of bone
- Extramedullary plasmacytoma
- POEMS syndrome
- Plasma cell leukaemia
- Heavy chain disease
- Monoclonal gammopathy of undetermined significance
- Smoldering multiple myeloma.

Q. Discuss the immunopathology, pathology, clinical features, investigations and treatment of multiple myeloma.

- Multiple myeloma is a malignant proliferation of plasma cells derived from a single clone.
- Plasma cells are derived from B lymphocytes. Individual plasma cells produce immunoglobulins with only one type of light chain (kappa or lambda).
- It is believed that most cases are preceded by a phase of monoclonal gammopathy of undetermined significance.

Immunopathology

- Multiple myeloma is "monoclonal"—i.e. the tumour is derived originally from one cell by cloning. So, all the malignant cells produce the same immunoglobulin.
- The immunoglobulin produced is called a "paraprotein" (M-protein). It appears on electrophoretic strip as a clear-cut band (M-band or M-component).
- In myeloma, the paraprotein produced belongs to one of the immunoglobulin types and has one or other of the two light chains—i.e. kappa or lambda.
- In Bence–Jones or light-chain myeloma, only the light chains are produced in excess, and not the whole immunoglobulin molecule. These excess light chains appear in the urine as Bence–Jones proteinuria.
- Classification of myeloma is based on the type of paraprotein produced—i.e. IgG (55%), IgA (25%), IgD (uncommon), IgE (uncommon), and light chain disease (20%). In non-secretory myeloma, there is no M-protein in the blood or urine but has bone marrow plasmacytosis and organ or tissue impairment.

POEMS Syndrome

- A variant of multiple myeloma is POEMS syndrome; the acronym stands for polyneuropathy, organomegaly (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic), endocrinopathy, M-protein (usually IgG or IgA lambda light chain) and skin changes (hyperpigmentation, hypertrichosis, acrocyanosis, white nails, scleroderma-like changes, facial atrophy, flushing, or clubbing). Other common features not included in this acronym include oedema, ascites, pleural effusion, osteosclerotic bone lesions, thrombocytosis, increased risk of arterial or venous thrombosis, paipilloedema and a high level of serum vascular endothelial growth factor (VEGF). Autologous peripheral blood stem cell transplantation is the treatment of choice for younger patients. In older patients, melphalan and dexamethasone are considered. In localised disease without clonal plasma cells in bone marrow biopsy, local radiation is recommended.

Pathology and Pathogenesis

- Bone marrow is infiltrated heavily with atypical plasma cells. Gradual replacement of the marrow by plasma cells results in anaemia, leucopenia and thrombocytopenia.
- In majority of patients, plasma cells are seen in the peripheral blood in small numbers. In a few patients, plasma cells are seen in the peripheral blood in significant numbers (more than 2000/mm^3), and this condition is known as "plasma cell leukaemia".
- Localised tumour formation results in punched-out lesions on radiographs of flat bones.
- Serum uric acid is elevated due to increased cell turnover.
- Osteoclasts are stimulated resulting in bone resorption and generalised osteoporosis.
- Mobilisation of calcium from bone results in hypercalcaemia, hypercalciuria and nephrocalcinosis.
- Bence–Jones proteinuria, amyloidosis, hypercalcaemia and hyperuricaemia result in renal damage and renal failure.
- Hyperviscosity syndrome results from increased viscosity of blood and is more common in IgA subtype of multiple myeloma.

Clinical Features

- Peak incidence is between 60 and 70 years, and males are more affected than females.
- Some patients are asymptomatic, and myeloma is accidentally detected during the preclinical phase.
- Some patients develop extramedullary masses of malignant plasma cell known as plasmacytomas. These may be present at the time of diagnosis of multiple myeloma or may develop later during its course. Para-skeletal soft tissue is the most common (80%) site of plasmacytoma. Other areas include gut, skin, airways, liver, kidneys, CNS and breast. In a patient with multiple myeloma, presence of plasmacytomas indicate poor prognosis. Palliative radiotherapy is indicated for controlling symptoms related to plasmacytomas. Lenalidomide (and not thalidomide) and bortezomib have some role in management of plasmacytomas.
- Patients with multiple myeloma may go onto develop primary amyloidosis, plasmacytomas, heavy-chain disease or plasma cell leukaemia.

Bone marrow involvement	Anaemia, leucopenia and thrombocytopenia
Bone involvement	Localised bony swellings over vertebrae, skull, sternum, ribs and clavicle, bone pain due to pathological fractures, and compressive myelopathy due to vertebral collapse and compression
Renal involvement	Nephrocalcinosis, amyloidosis and progressive renal failure
Immune system involvement	Increased susceptibility to infections, particularly of the respiratory system and urinary tract
Hyperviscosity syndrome	Blurred vision with retinal venous congestion, papilloedema, headache, vertigo, nystagmus, postural hypotension and congestive cardiac failure
Clotting problems	Purpura, epistaxis, gastrointestinal bleeding
Neurological manifestations	Amyloid peripheral neuropathy, carpal tunnel syndrome, compressive myelopathy and radiculopathy

Diagnosis

- Diagnosis of multiple myeloma requires the detection of at least two of the following:
  - Monoclonal immunoglobulin or light chains in the blood (>3 g/dL) or urine.
  - Infiltration of bone marrow with malignant plasma cells (≥10%).
  - Evidence of myeloma-related organ or tissue impairment (≥1) – *CRAB*:
    - *C*alcium serum (ionized) >5.5 mEq/L.
    - *R*enal insufficiency (creatinine >2 mg/dL).
    - *A*naemia (haemoglobin <10 g/dL).
    - *B*one involvement—osteolytic bone lesions and/or osteopenia.
- Light-chain multiple myeloma:
  - Same as MM except no evidence of Ig heavy-chain expression on immunofixation.
  - Around 20% of patients with myeloma produce only light chains in the serum and urine
- Around 2% produce neither light chains nor a paraprotein and are termed non-secretors. In such cases, >30% monoclonal plasma cells in bone marrow are required to make a diagnosis of myeloma.

Smouldering or Asymptomatic Multiple Myeloma

- Characterised by M-component >3 g/dL and/or clonal bone marrow plasma cells ≥10%, without myeloma-related organ or tissue impairment.
- Progresses to multiple myeloma or AL amyloidosis at a rate of 10% per year in the first 5 years, and at a lower rate after that.
- Serum protein electrophoresis, complete blood count, measurement of calcium and creatinine values and 24-hour urine collection for electrophoresis and immunofixation should be performed at diagnosis and in 2–3 months after the initial recognition. A skeletal survey and bone marrow are mandatory at baseline. If the results at 2–3 months are stable, the studies should be repeated every 4–6 months for 1 year and, if stable, evaluation can be lengthened to every 6–12 months.

Investigations

- Haemogram usually shows anaemia, leucopenia, thrombocytopenia and raised ESR (often >100).
- Peripheral blood smear may show rouleaux formation.
- Bence–Jones proteins may be present in the urine.
- Urea, creatinine and electrolytes are used to assess renal function.
- Serum calcium level is usually raised.
- Serum uric acid level is elevated.
- Serum alkaline phosphatase is characteristically normal, in the absence of complications.
- Total serum protein level is increased, albumin is decreased and globulins are markedly increased.
- Serum immunoglobulin estimation reveals a reduction of normal immunoglobulins below normal levels.
- Serum β_2-microglobulin level may provide a useful assessment of prognosis. Higher levels indicate poor prognosis.
- Radiological examination reveals generalised osteoporosis. Radiographs of flat bones like skull, vertebral bodies, ribs and pelvis show the characteristic punched-out osteolytic lesions. Collapse of multiple vertebrae is a common radiological finding.
- Electrophoretic studies can demonstrate the paraprotein on the electrophoretic strip as the "M-band". Immunoelectrophoresis and immunofixation can determine the immunoglobulin type, and confirm that the M-component is truly monoclonal.
- MRI and PET may detect bone involvement when skeletal survey is normal.
- Bone scan is not required as it is often negative (may show increased uptake if a fracture of bone develops).
- Bone marrow examination is important. Normal bone marrow contains 2–10% plasma cells. In myeloma, the number of plasma cells is increased, and they are atypical in morphology.
- Confirmation of clonality of plasma cells in bone marrow by immunophenotyping with flow cytometry or immunohistochemistry.

Staging

Durie–Salmon Staging

Stage	Criteria

• Stage I	All of the following:
	• Haemoglobin >10 g/dL
	• Serum calcium <12 mg/dL
	• Normal skeletal X-rays or only solitary lesion
	• Low M-component:
	  • IgG <5 g/dL
	  • IgA <3 g/dL
	• Urine light chain <4 g/24 hours

• Stage II	Not fitting into stage I or III

• Stage III	One or more of the following:
	• Haemoglobin <8.5 g/dL
	• Serum calcium >12 mg/dL
	• Advanced lytic lesions on X-rays
	• High M-component:
	  • IgG >7 g/dL
	  • IgA >5 g/dL
	• Urine light chain >12 g/24 hours

Subclassification based on serum creatinine levels • Creatinine <2 mg/dL—Subclass A • Creatinine >2 mg/dL—Subclass B	

International Staging System

- It has largely replaced Durie-Salmon staging system

Stage	Definition	Median survival
• Stage I	Albumin >3.5 g/dL and β_2-microglobulin <3.5 mg/dL	60 months
• Stage II	Albumin <3.5 g/dL and β_2-microglobulin <3.5 mg/dL or β_2-microglobulin 3.5–5.5 mg/dL	42 months
• Stage III	β_2-microglobulin >5.5 mg/dL (regardless of albumin level)	27 months

Treatment

- Median survival in patients with advanced myeloma is 7–8 months. With chemotherapy, this can be prolonged to 3-4 years. There is no cure available till now.
- Asymptomatic stage I patients are generally not given chemotherapy.
- Prognosis relies not only on staging but also to a large extent on the cytogenetic features.

General Measures

- Prompt treatment of infections.
- Treatment of anaemia.
- High fluid intake of about 3 L/day.
- In patients with compromised renal function, sodium bicarbonate may be given orally to make the urine alkaline.
- Allopurinol 300 mg daily should be given to reduce hyperuricaemia.
- Analgesics should be given for pain relief.
- Expert orthopaedic assistance and skilled physiotherapy can significantly improve the quality of life.
- Renal failure should be treated medically, with dialysis if necessary.
- Hypercalcaemia may be treated by rehydration and oral prednisolone. Mithramycin is highly effective in controlling hypercalcaemia, but is highly toxic. A better option is to give pamidronate (15–30 mg as slow infusion).
- Hyperviscosity syndrome is managed by plasmapheresis.

Stem Cell Transplantation

- Treatment of choice in multiple myeloma in eligible patients
- Induction therapy with one of the combinations as given in the box under 'Treatment Regimens' followed by consolidation regimen using high-dose melphalan (200 mg/m^2) intravenously and then autologous stem cell transplantation is the standard treatment in young patients (<65 years) without renal failure.

Drug Therapy

- Currently, 5 classes of active agents are available: alkylating agents (melphalan and cyclophosphamide), anthracyclines (adriamycin and liposomal doxorubicin), corticosteroids (dexamethasone and prednisone), immunomodulatory drugs (thalidomide, lenalidomide and pomalidomide), and proteasome inhibitors (bortezomib and carfilzomib).
- Steroid (dexamethasone or prednisolone) use is pivotal in the treatment of multiple myeloma and is generally included in all treatment regimens.
- Bortezomib is essential in patients with high-risk cytogenetic features.
- Immunomodulating drugs like thalidomide, lenalidomide and pomalidomide along with prednisolone or dexamethasone produces remission in about 60-70% patients.
- Bortezomib, when combined with lenalidomide and dexamethasone may produce remission in >90% cases. Its side effects include thrombocytopenia, neutropenia, diarrhoea and sensory neuropathy. Reactivation of varicella zoster virus may occur.

Treatment Regimens

Stem cell transplant eligible:
- Lenalidomide/dexamethasone
- Bortezomib/dexamethasone
- Bortezomib/lenalidomide/dexamethasone
- Bortezomib/cyclophosphamide/dexamethasone
- Bortezomib/doxorubicin/dexamethasone
- Bortezomib/Thalidomide/dexamethasone

Stem cell transplant ineligible:
- Melphalan/bortezomib/dexamethasone
- Melphalan/thalidomide/dexamethasone
- Lenalidomide/dexamethasone
- Melphalan/prednisolone/lenalidomide

Radiotherapy

- Ideal for local problems like severe bone pain, pathological fractures and tumourous lesions.

Miscellaneous

- Bisphosphonates (pamidronate, zoledronic acid, clodronate) reduce the incidence of vertebral fractures and ameliorate pain, and should be considered in stage II and III disease. Bisphosphonates inhibit osteoclast recruitment and maturation, prevent the development of monocytes into osteoclasts, induce osteoclast apoptosis and interrupt their attachment to the bone. However, they do not have any effect on overall survival, hypercalcaemia or incidence of non-vertebral fractures. An important complication of bisphosphonates is osteonecrosis of jaw.
- Patients started on immunomodulatory treatment (thalidomide or lenalidomide) have increased risk of venous thrombosis. Hence, they should receive aspirin or low molecular weight heparin.

Q. What are the causes of M-component on electrophoresis?

Conditions that can have M-Component

Plasma cell disorders

- Multiple myeloma
- Waldenstrom macroglobulinaemia
- Primary amyloidosis
- Heavy chain disease
- MGUS

Other lymphoid neoplasms
- Chronic lymphatic leukaemia
- Lymphomas

Non-lymphoid neoplasms
- Chronic myeloid leukaemia
- Breast carcinoma

Non-neoplastic conditions
- Cirrhosis of liver
- Sarcoidosis
- Rheumatoid arthritis
- Myasthenia gravis

Q. What are the causes of renal failure in multiple myeloma?

- Frank renal failure is seen in about 25% of multiple myeloma patients.
- Some form of renal pathology can be observed in 50% of myeloma patients.
- Various factors contributing to renal failure in multiple myeloma are the following:
  - Tubular damage (cast nephropathy) from excretion of light chains (Bence-Jones proteinuria).
  - Hypercalcaemia resulting in nephrocalcinosis and renal damage.
  - Glomerular deposition of amyloid (renal amyloidosis).
  - Hyperuricaemia resulting in urate nephropathy.

- Recurrent urinary infections.
- Infiltration of the kidney by myeloma cells.
- Hyperviscosity syndrome
- Use of nephrotoxic drugs (e.g. NSAIDs for bone pains).
- Monoclonal gammopathy of renal significance (MGRS) is defined by causal relationship between a small B-cell clone and renal disease, usually through deposition of the secreted monoclonal immunoglobulin or its fragment. It is separate from the causes of renal failure in multiple myeloma mentioned above.

Q. What are the indicators of poor prognosis in multiple myeloma?

• Low haemoglobin (<8.5 g/dL)	• Renal failure
• Serum calcium >12 g/dL	• Thrombocytopenia
• Elevated β_2-microglobulin	• Advanced lytic bone lesions
• Lambda light chain secretors	• Plasma cell leukaemia

Q. Discuss the role of radiographic examination in the diagnosis of multiple myeloma.

• X-ray skull	Multiple punched out osteolytic lesions and osteoporosis
• X-ray chest	Pathological fractures of ribs, punched out lesions of ribs, clavicle and scapulae, and osteoporosis
• X-ray spine	Collapse of multiple vertebrae and osteoporosis
• X-ray pelvis	Multiple punched out osteolytic lesions and osteoporosis
• X-ray KUB	Nephrocalcinosis

Q. What is monoclonal gammopathy of undetermined significance (MGUS)?

- Premalignant clonal disorder is characterised by M-component on electrophoresis but <3 g/dL, plasma cells <10% in bone marrow, no hypercalcaemia, renal impairment, anaemia or osteolytic lesions, no light-chain amyloidosis or evidence of other B-cell neoplasms.
- Present in more than 3% of the general population above the age of 50 years.
- Progresses to multiple myeloma, Waldenstrom's macroglobulinaemia, primary AL amyloidosis, or a lymphoproliferative disorder at a rate of 1–1.5% per year.
- Risk of progression to multiple myeloma and related disorders depends upon size of M-component (risk of progression with an M-protein value of 1.5 g/dL almost twice that of a patient with an M-protein value of 0.5 g/dL), type of M-component (IgM and IgA increased risk compared to IgG), and an abnormal free light chain ratio (kappa : lambda ratio—normal being 0.26–1.65).
- Patients should be followed with serum protein electrophoresis at 6 months and, if stable, can be followed every 1–2 years depending upon risk of progression or when symptoms suggestive of a plasma cell malignancy arise.
- No treatment is indicated.

Q. How do you differentiate between multiple myeloma and monoclonal gammopathy of undetermined significance (MGUS)?

	Multiple myeloma	MGUS
• M-protein level in serum	M-protein found in serum and/or urine except in patients with non-secretory myeloma	<3 g/dL with expression of intact immunoglobulin (e.g. IgG, IgM, IgA)

	Multiple myeloma	MGUS
• Bone marrow	Clonal plasma cells ≥10% or Presence of plasmacytomas	Clonal plasma cells <10% No evidence of other B-cell proliferative disorders
• Organ/tissue involvement	At least one of the following: • Calcium (ionised) >5.5 mEq/L • Renal insufficiency (creatinine >2 mg/dL) • Anaemia (haemoglobin <10 g/dL) • Bone involvement—osteolytic bone lesions and/or osteopenia	No hypercalcaemia, renal impairment, anaemia, bone involvement

Q. Describe solitary plasmacytoma of bone.

- Localised accumulation of neoplastic monoclonal plasma cells to a single bone at presentation without a proof of a systemic plasma cell proliferative disorder.
- Represents 3% of plasma cell neoplasms.
- Primarily affects the axial skeleton, most commonly thoracic or lumbosacral vertebrae, causing localised bone pain or neurologic symptoms secondary to spinal cord or root compression.
- Diagnosis requires solitary bone lesion confirmed by skeletal survey, plasma cell infiltration proven by biopsy, normal bone marrow biopsy (<10% plasma cells), and lack of myeloma-related organ dysfunction.
- Low levels of serum or urine M protein detectable in 24% to 60% of patients by immunofixation.
- Nearly 70% eventually develop systemic disease at a median of 2 to 4 years despite radiation treatment.
- Treatment is local radiotherapy.
- Overall median survival is 7 to 12 years.

Q. What is solitary extramedullary plasmacytoma?

- Occurs most commonly (85%) in head and neck region, followed by gastrointestinal tract.
- More than 75% of the tumours do not produce detectable serum M protein.
- Diagnosis requires tissue biopsy indicating monoclonal plasma cell histology, bone marrow plasma cell infiltration <5% of all nucleated cells, absence of osteolytic bone lesions or other tissue involvement and lack of myeloma-related organ dysfunction.
- Nearly 15% of patients subsequently develop multiple myeloma.
- Low levels of serum or urine M protein may be detectable in some cases.
- Treatment requires local removal. However, since most cases occur in head and neck area, surgery may not be a feasible option. In such cases, local radiotherapy is recommended.
- Median 10-year survival rate approximately 70% compared with 40% in solitary plasmacytoma of bone.

Q. What is plasma cell leukaemia?

- An aggressive disease associated with a high tumour burden and extramedullary dissemination.
- Defined as an absolute plasma cell count >2,000/dL or plasma cells comprising more than 20% of total leucocytes in the peripheral blood.
- Primary plasma cell leukaemia develops without any preceding evidence of multiple myeloma while secondary plasma cell leukaemia occurs as a terminal stage of multiple myeloma.

Clinical Features

- Symptoms due to anaemia, hypercalcaemia or bleeding diathesis owing to thrombocytopenia.
- Organomegaly with involvement of liver, spleen, lymph nodes
- Pleural effusion
- Neurological deficits
- Extramedullary soft-tissue plasmacytomas
- Tumour lysis syndrome

Q. Give a brief account of Waldenstrom macroglobulinaemia.

- It is a B-cell lymphoproliferative disorder characterised by a lymphoplasmacytic infiltration in the bone marrow or lymphatic tissue and a monoclonal immunoglobulin M protein (IgM) in the serum.
- Classified as lymphoplasmacytic lymphoma under WHO classification of non-Hodgkin's lymphoma.
- Occurs in older adults.

Clinical Features

- May be asymptomatic.
- Symptoms develop due to tumour infiltration (cytopenia, fever, night sweats, weight loss, lymphadenopathy, organomegaly) and/or monoclonal protein (hyperviscosity, cryoglobulinaemia, cold agglutinin, neuropathy, and amyloidosis).
- Circulating IgM can be associated with type I cryoglobulinaemia or coagulation abnormalities due to coating of coagulation factors by IgM.
- Tissue deposition of monoclonal IgM is associated with systemic amyloidosis, macroglobulinaemia cutis, gastrointestinal symptoms (malabsorption, diarrhoea or bleeding) and glomerular injury.
- Monoclonal IgM can also produce haemolytic anaemia (due to cold agglutinin disorder), small vessel vasculitis and peripheral neuropathy.
- Hyperviscosity occurs due to large size of IgM molecule. It is most commonly manifested by bleeding (epistaxis, gingival bleeding), blurring or loss of vision, dizziness, headache, vertigo, nystagmus, hearing loss, ataxia, paraesthesias, diplopia, somnolence and coma.
- Peripheral neuropathy is present in near 20% patients. This is usually a distal, symmetric, chronic, demyelinating neuropathy, sometimes associated with abnormalities of proprioception and ataxia.
- Tumour cells can infiltrate organs and result in hepatomegaly, splenomegaly and lymphadenopathy in about 20% cases.

Diagnosis

- Serum monoclonal protein detection by serum protein electrophoresis; samples may require warming to 37°C to avoid interference of cold agglutinins. Immunofixation is required to characterise monoclonal protein.
- Bone marrow aspirate and biopsy showing more than 10% lymphoplasmacytic cells (positive for CD19, CD20, CD22 and CD79a23).

Treatment

- The median survival is 5 years.
- Disease incurable with currently available therapies including rituximab and fludarabine.
- Fludarabine may predispose to late myelodysplasia and large-cell lymphoma transformation.

Asymptomatic	Early	Hyperviscosity	Advanced
• No compromise of vital organs • No bulky disease • Hb ≥11 g/dL • Platelets ≥1,20,000/mm³	• Modest haematologic compromise • IgM-related neuropathy • Haemolytic nanemia		• Severe constitutional symptoms • Hb <10 g/dL • Platelets <1,00,000/mm³ • Bulky disease

Plasmapheresis

| Observation | Rituximab | | • Dexamethasone, rituximab and cyclophosphamide OR
• Rituximab plus fludarabine |

Q. Briefly outline the side effects, precautions and dosage of thalidomide.

- Introduced initially for the treatment of morning sickness in pregnant females but was withdrawn in 1960s because of reports of teratogenicity associated with its use, particularly limb defects or phocomelia. The typical feature is defective, shortened limbs resulting in flipper hands and feet. In more severe cases, complete absence of limbs can occur. Additionally, foetus can develop external ear abnormalities, hypoplastic or completely absent bones, facial palsy, eye abnormalities, and gastrointestinal and genitourinary tract malformations.
- Later, it was found to inhibit angiogenesis and possess immunomodulatory and anti-inflammatory properties.

Side effects	
• Peripheral nerves	Numbness, tingling, burning sensation
• Central nervous system	Tremors, confusion, fatigue, depression, somnolence, headache, bradycardia
• Gastrointestinal	Constipation, nausea, dry mouth, increased appetite
• Haematological	Deep vein thrombosis, neutropenia
• Skin	Skin rash, itching, red palms
• Endocrine	Hypothyroidism
• Pregnancy	Phocomelia

Precautions

- It is important to remember that even a single dose of thalidomide can produce congenital malformations. Therefore, effective contraception must be used at least 4 weeks before beginning thalidomide therapy, during thalidomide therapy, and for 4 weeks following discontinuation of thalidomide therapy.
- Once treatment has started, pregnancy testing should occur weekly during the first 4 weeks of use, then pregnancy testing should be repeated at 4 weeks in women with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks.

Dose

- Initially 200 mg/day, increased to 400–600 mg/day with increment of 100 mg/week.

Uses

Established	Potential
• Multiple myeloma	• Myelodysplastic syndrome (MDS) (with refractory cytopenias)
• Erythema nodosum leprosum	• Waldenstrom's macroglobulinaemia
• Myelofibrosis with myeloid metaplasia	• Solid organ tumours
	• Behcet disease
	• Pyoderma gangrenosum
	• Graft-versus-host disease (GVHD)

Q. Discuss the mechanism of haemostasis.

Q. Write in brief about platelets and their functions.

Q. Briefly outline the natural inhibitors of coagulation.

Q. Describe fibrinolytic system.

- Haemostatic mechanism is responsible for prevention of blood loss from intact vessels, as well as for the arrest of bleeding from injured vessels.
- It is activated by damage to the vascular endothelium and exposure of subendothelial tissue to blood.

Mechanism of Haemostasis

- Three major components of the normal haemostatic mechanism—the vascular component, the platelet component, and the coagulation component. The first two components are called primary haemostasis while the last component is called secondary haemostasis.
- A defect in any one of these three results in an abnormal tendency to bleed—i.e. bleeding disorder. The defect may be either quantitative (deficiency) or qualitative (functional).
- Venous thrombi, which form under low flow conditions, are predominantly composed of fibrin and red cell.
- Arterial thrombosis is usually initiated by spontaneous or mechanical rupture of atherosclerotic plaque, a process that exposes thrombogenic material in the lipid-rich core of the plaque to the blood. These thrombi form under high shear conditions and are primarily composed of platelet aggregates held together by fibrin strands.

Vascular Component

- This involves a reflex spasm of the injured vessel (vasoconstriction) that serves to minimise blood loss.

Platelet Component

- Platelets are derived from marrow megakaryocytes. They are anucleate and have a discoid shape. The normal lifespan is about 10 days. The normal blood platelet count ranges from 150,000 to 450,000/μL. About 70% of the platelets are in circulation while 30% are in the spleen.
- The cytoplasm of platelets contain three major types of storage granules:
  - α-granules containing a variety of proteins like fibrinogen and von Willebrand factor.
  - Dense granules containing serotonin, ADP (which helps in platelet aggregation) and calcium.
  - Lysosomal granules containing acid hydrolases.
- The platelet component requires three critical events—platelet adhesion, release of granule contents and platelet aggregation.
- Following vessel constriction, platelets adhere to the vessel wall by two collagen receptors present on platelets—glycoprotein Ib (GpIb) and glycoprotein VI (GpVI). This is facilitated by:
  - Factor VIII-von Willebrand factor released from damaged endothelial cells that form a link between platelet glyco-proteins and exposed collagen.
  - Exposed subendothelial collagen tissue.
  - Release of ADP and thromboxane A_2.
- Platelet activation follows adhesion and results in the discharge of the granule content. Binding of collagen, epineph-rine and thrombin to platelets also activates phospholipase A_2 and phospholipase C on the membrane of platelets which catalyses the release of arachidonic acid from two membrane phospholipids (phosphatidylinositol and phospha-tidylcholine). The enzyme cyclooxygenase then converts arachidonic acid into endoperoxides. These are converted to thromboxane A_2 by thromboxane synthetase and prostacyclin by prostacyclin synthetase. Thromboxane A_2 is a potent stimulant of platelet activation and aggregation while prostacyclin inhibits activation.

Arachidonic Acid Pathway
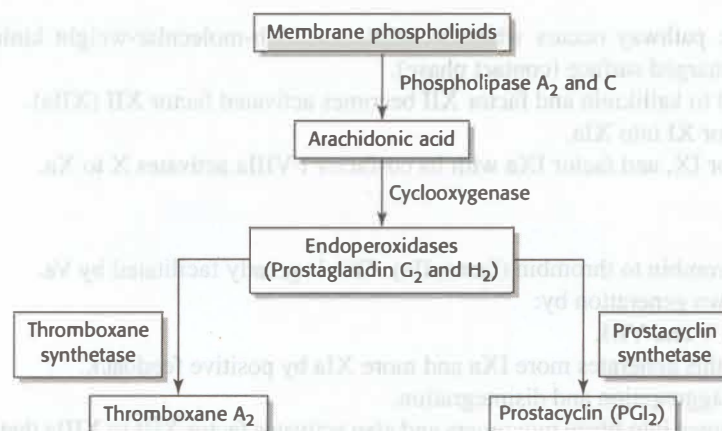
- Platelet aggregation (adhesion of activated platelets to each other) is facilitated by fibrinogen forming links among adjacent platelets via glycoprotein IIb/IIIa (GPIIb/IIIa).
- Platelet adhesion and platelet aggregation serve to form a platelet plug that seals off the vascular breach and arrests haemorrhage.

Functions of Platelets

- Platelets maintain vascular integrity.
- Platelets can spontaneously arrest bleeding through platelet plug formation.
- Platelets participate in the intrinsic coagulation system.
- Platelets promote repair and healing through release of growth factors.

Coagulation Component (secondary haemostasis)

- During secondary haemostasis, the platelet plug is stabilised by the deposition of a network of fibrin formed through the activation of coagulation cascade.

Components of the Coagulation Cascade

Coagulation Cascade

- Coagulation cascade can be conveniently considered under three "pathways": the intrinsic pathway (contact activation pathway), the extrinsic pathway (tissue factor pathway) and the common pathway.
- Intrinsic pathway and extrinsic pathway are alternative routes to the production of factor Xa (activated X) with extrinsic pathway being the primary pathway.
- Common pathway is the process initiated by factor Xa leading to the production of fibrin.
- Intrinsic pathway is assessed in vitro by the activated partial thromboplastin time (aPTT).
- Extrinsic pathway is assessed by the prothrombin time (PT).

Factor	Synonym	Factor	Synonym
• I	Fibrinogen	• IX	Christmas factor
• II	Prothrombin	• X	Stuart–Prower factor
• V	Proaccelerin	• XI	Plasma thromboplastin antecedent
• VII	Proconvertin	• XII	Hageman factor
• VIII	Antihaemophilic factor	• XIII	Fibrin stabilising factor

Extrinsic Pathway

- "Tissue factor" (a protein-phospholipid complex normally present on vascular cells and activated monocytes) converts factor VII into activated factor VII (VIIa) in presence of calcium.
- Activated tissue factor VII complex activates factors IX and X.

Intrinsic Pathway

- Initiation of the intrinsic pathway occurs when prekallikrein, high-molecular-weight kininogen and factor XII are exposed to a negatively charged surface (contact phase).
- Prekallikrein is converted to kallikrein and factor XII becomes activated factor XII (XIIa).
- Factor XIIa converts factor XI into XIa.
- Factor XIa activates factor IX, and factor IXa with its co-factor FVIIIa activates X to Xa.

Common Pathway

- Factor Xa converts prothrombin to thrombin (factor IIa). This is greatly facilitated by Va.
- Thrombin enhances its own generation by:
  - Activating the factors V and VIII.
  - Activating factor XI, this generates more IXa and more XIa by positive feedback.
  - Encouraging platelet aggregation and disintegration.
- Factor IIa converts fibrinogen into fibrin monomers and also activates factor XIII to XIIIa that cross-links fibrin to fibrin polymers.

Intrinsic pathway

High molecular weight kininogen (HMWK)
Prekallikrein
Factor XII (Hageman factor)

XII ⟶ XIIa

XI ⟶ XIa   Thrombin

VIIIa ⟵ VIII
Ca^{++}
Platelets

X ⟶ Xa

Extrinsic pathway

Tissue trauma

Tissue factor (tissue thromboplastin)

VII ⟶ VIIa

X ⟶ Xa

Common pathway

Xa
Ca^{++}
Platelets
Va ⟵ V   XIII

Prothrombin   Thrombin ⟵ XIIIa

Fibrinogen ⟶ Fibrin   ⟶ Stabilised
                monomers   (cross-linked fibrin)
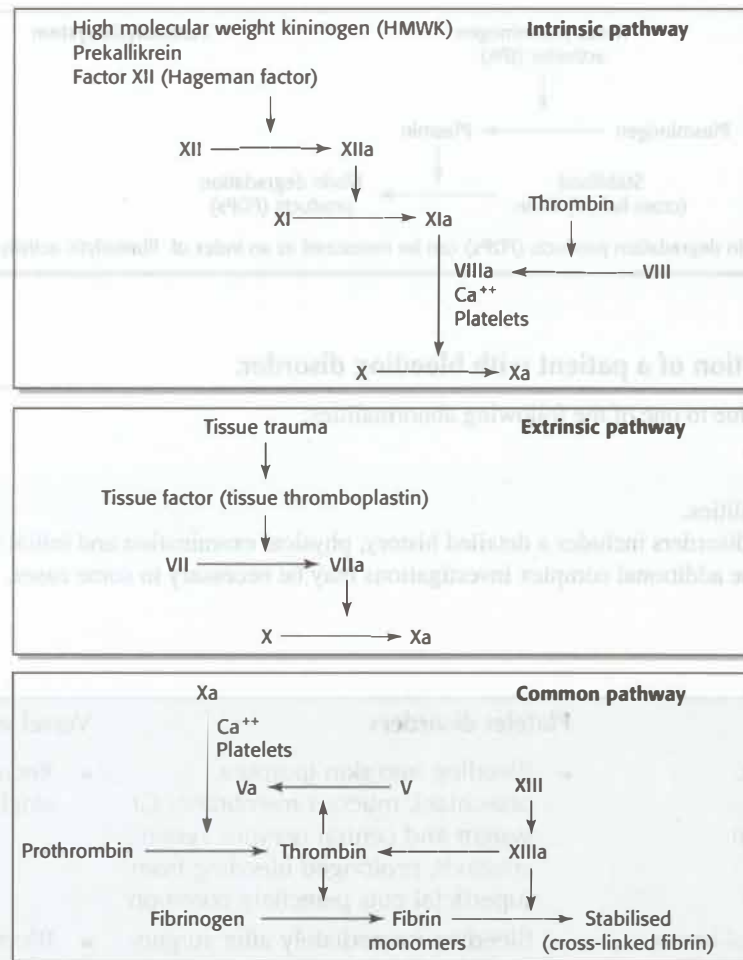
Inhibitors of Coagulation

- Natural inhibitors of coagulation provide a mechanism to limit clotting to the vicinity of tissue injury.

- Antithrombin
- Heparin co-factor II
- Alpha$_2$-macroglobulin
- Protein C and protein S

- Antithrombin, a circulating serine protease inhibitor (serpin) inactivates thrombin, IXa, Xa and XIa. Its action is potentiated by heparin sulphate released from endothelium. Heparin also increases its action.
- Protein C, activated by the thrombin–thrombomodulin complex, inactivates Va and VIIIa in the presence of the activated cofactor Protein S. Impaired activity of protein C occurs in factor V Leiden, produces thrombophilia.
- Endothelial cells also produce prostacyclin and nitric oxide that inhibit platelet aggregation.

Fibrinolytic System

- Physiological function of the fibrinolytic system is to digest deposits of fibrin (thrombi). The defect in the vessel wall then becomes covered with endothelial cells.
- Tissue plasminogen activator is released from endothelial cells following injury and in response to thrombin.
- It cleaves plasmin from plasminogen bound to fibrin within the clot.
- Kallikrein also activates plasmin from plasminogen.
- Plasmin degrades fibrin into D-dimers and fibrin degradation products (FDP). It also degrades Va, VIIIa and GPIb.
- Fibrinolysis is controlled by release of plasminogen activator inhibitor 1 (PAI-1) from platelets. PAI-1 is inhibited by activated protein C. Other inhibitors of fibrinolysis include α_2-antiplasmin and α_2-macroglobulin.

```
                        Tissue plasminogen              Fibrinolytic system
                         activator (tPA)

                              │
                              ▼
        Plasminogen ─────────────────► Plasmin

                              │
                              ▼
          Stabilised                        Fibrin degradation
        (cross-linked) fibrin ────────────► products (FDPs)

        Fibrin degradation products (FDPs) can be measured as an index of fibrinolytic activity
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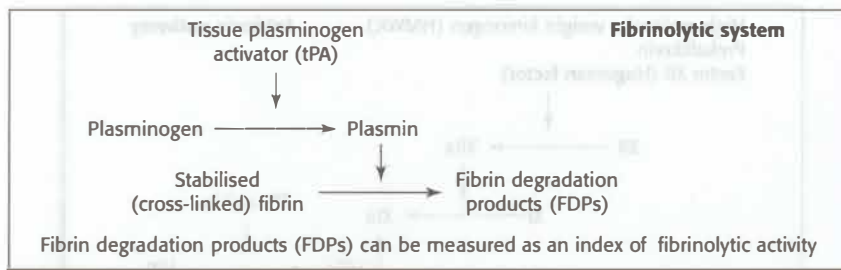
Q. Discuss the evaluation of a patient with bleeding disorder.

- Bleeding disorders are due to one of the following abnormalities:
  - Coagulation defects.
  - Platelet disorders.
  - Vessel wall abnormalities.
- Evaluation of bleeding disorders includes a detailed history, physical examination and initial screening tests. Based on the results of these, some additional complex investigations may be necessary in some cases.

History

Coagulation defects	Platelet disorders	Vessel wall abnormalities
• Bleeding into viscera, muscles and joints; petechiae uncommon	• Bleeding into skin (purpura, petechiae), mucous membrane, GI system and central nervous system; epistaxis; prolonged bleeding from superficial cuts petechaie common	• Recurrent bleeding at a single site
• Bleeding starts several hours after surgery or trauma	• Bleeding immediately after surgery or trauma	• Bleeding occurs immediately after trauma
• Local pressure ineffective	• Local pressure effective	• Local pressure effective
	• History of drug intake, especially non-steroidal anti-inflammatory drugs like aspirin	

Congenital defects
- Lifelong history
- Family history

Acquired defects
- Short duration
- Evidence of liver disease, renal failure, disseminated intravascular coagulation (DIC)

Physical Examination

- Physical examination should include a diligent search for the following:
  - Purpura, bruises, and ecchymoses.
  - Telangiectasia in hereditary haemorrhagic telangiectasias.
  - Scars over elbows and knees in factor XIII deficiency.
  - Examination of joints, particularly knees, ankles and elbows for haemarthrosis.
  - Signs of liver cell disease.
  - Hepatosplenomegaly and lymphadenopathy.
  - Neurological signs.

Screening Tests

Screening test	Components assessed
• Peripheral smear	Platelets, leucocytes, red blood cells
• Platelet count (N: 150 to 350 $\times$ 10^3/mm^3)	Platelets
• Bleeding time (N: <9 minutes)	Platelet function, von Willebrand factor
• Prothrombin time (N: 12–14 seconds)	Extrinsic pathway, factors V, VII, X; factor I, II
• Activated partial thromboplastin time (N: 33–45 seconds)	Intrinsic pathway, factors V, VIII, IX, X, XI, XII; factor I, II
• Thrombin time (N: 12–16 seconds)	Common pathway, factors I, II
• Clot retraction	Platelets
• Fibrinogen concentration (N: 150–450 mg/dL)	Fibrinogen
• Fibrin degradation products (FDPs)	Lysis of fibrin

Bleeding Time

- Prolonged in platelet disorders.
- Ivy's method:
  - Tie a blood pressure cuff around the upper arm and inflate it to 40 mmHg to block venous return.
  - Clean the skin of the forearm and make two puncture marks using a lancet.
  - Soak the oozing blood every 15 seconds with a filter paper until bleeding stops.
  - Normal bleeding time <9 minutes.

Prothrombin Time

- Normal is within 3 seconds of control value (12–14 seconds).
- Prolonged in deficiency of fibrinogen (factor I) factor II, V, VII and X, liver disease, DIC, vitamin K deficiency, oral warfarin therapy and in presence of anti-phospholipid syndrome.

Activated Partial Thromboplastin Time

- Normal PTT is 33–45 seconds.
- Prolonged in deficiency of factors I, II, V, VIII, IX, X, XI and XII, including haemophilia A and B, von Willebrand disease, DIC, heparin therapy, and presence of lupus anticoagulant and acquired factor inhibitors.

Q. Define thrombocytopenia. Enumerate the common causes, clinical manifestations, investigations and management of thrombocytopenia.

Q. Describe Tourniquet test (capillary resistance test of Hess; Hess test).

Q. Enumerate the common conditions inhibiting platelet function or qualitative platelet disorders.

Definition

- Thrombocytopenia is defined as a platelet count below 100,000/mm^3.

Causes

Decreased production
• Marrow aplasia/hypoplasia—e.g. idiopathic, drugs, alcohol
• Marrow fibrosis—e.g. myelofibrosis
• Marrow infiltration—e.g. leukaemia, myeloma, carcinoma
• Vitamin B$_{12}$ and folate deficiency

Increased destruction

- Non-immunologic thrombocytopenia—e.g. vasculitis, DIC, thrombotic thrombocytopenic purpura (TTP), haemolytic uraemic syndrome (HUS), HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome, vascular prosthesis
- Immunologic thrombocytopenia—e.g. idiopathic thrombocytopenic purpura (ITP), viral and bacterial infections (including HIV, hepatitis C infection; *Helicobacter pylori*; transient in infections with dengue, cytomegalovirus, Epstein–Barr virus), drugs (heparin, penicillin, quinine, quinidine, methyldopa), SLE, heparin-induced thrombocytopenia (HIT), post-transfusion
- Hypersplenism—portal hypertension, lymphomas, myeloproliferative disorders
- Dilutional—massive blood transfusion

General Clinical Manifestations

- Bleeding into skin—purpura, petechiae, ecchymoses.
- Bleeding into mucous membranes—epistaxis, haemorrhagic bullae in oral mucosa, genitourinary bleeding, gastrointestinal bleeding.
- Fundal haemorrhage and intracranial bleeding occur in severe thrombocytopenia.
- Tourniquet test (capillary resistance test of Hess; Hess test) may be positive. The sphygmomanometer cuff applied around the upper arm is inflated to a pressure halfway between systolic and diastolic blood pressures. The cuff is deflated after 5 minutes. Count the number of petechiae in an area of 3 cm diameter, 1 cm below the cubital fossa. A number exceeding 20 is interpreted as positive Hess test. Positive Hess test indicates increased capillary fragility resulting from thrombocytopenia.

- 150,000–450,000/mm^3 — Normal
- Less than 100,000/mm^3 — Thrombocytopenia
- Less than 50,000/mm^3 — Post-traumatic bleeding
- Less than 20,000/mm^3 — Spontaneous bleeding, fundal and intracranial bleeding

Investigations

- Peripheral blood smear:

Platelet clumping	Pseudothrombocytopenia
Giant platelets	Hereditary thrombocytopenia
Macrocytosis	Vitamin B$_{12}$ or folate deficiency
Schistocytes	Haemolytic uremic syndrome/thrombotic thrombocytopenic purpura; disseminated intravascular coagulation
Blasts, nucleated red cells	Probable primary bone marrow disorder
Lymphocytosis, neutrophilia, toxic granules in neutrophils	Probable infection
Isolated thrombocytopenia	Immune thrombocytopenic purpura, drug-induced thrombocytopenia, infections (HIV, hepatitis C, *Helicobacter pylori*), heparin-induced

- Platelet count is low. Clinical manifestations roughly correlate with the platelet count.
- Bleeding time (BT) is prolonged, and it bears a close relationship to platelet count.

- Bone marrow with normal or increased number of megakaryocytes indicates increased platelet destruction, hypersplenism or ineffective platelet production.
- Bone marrow with decreased number of megakaryocytes indicates reduced production of platelets.
- Investigations to look for the cause of thrombocytopenia.

Management

- Management is essentially the treatment of underlying cause (see causes).
- Severe bleeding, life-threatening situations like fundal haemorrhages and threatening intracranial haemorrhage can be temporarily treated with platelet transfusions.

Qualitative Platelets Defects

- Platelet function is impaired but counts remain normal.
- Most commonly due to drugs, some of which may also produce thrombocytopenia.

Drugs inhibiting platelet function or causing thrombocytopenia
- Non-steroidal anti-inflammatory drugs (NSAIDs)—aspirin, indomethacin
- Antibiotics—penicillins, cephalosporins, sulphonamides
- Heparin, dextran, β-blockers, quinidine, valproic acid, cimetidine.

Uraemia

Congenital disorders
- Disorders of membrane glycoproteins (Glanzmann thrombasthenia—deficiency or defect in GPIIb-IIIa, Bernard–Soulier syndrome—deficiency or defect in GPIb)
- Disorders of platelet secretion of ADP/prostaglandins (storage pool disorders)

Q. Discuss the pathogenesis, clinical features, investigations and management of immune (idiopathic) thrombocytopenic purpura (ITP).

Definition

- Immune (idiopathic) thrombocytopenic purpura (ITP) is thrombocytopenia (platelets $<1,00,000/mm^3$) due to an auto-immune disorder which occurs due to presence of autoantibodies directed against platelet membrane glycoproteins mainly GPIIb/IIIa and GPIb/IX.
- Since every patient may not have purpura, the term ITP is redefined as immune thrombocytopenia.

Pathogenesis

- About 85–95% of cases of ITP result from the presence of an antiplatelet antibody of IgG type. These antibody-bound platelets are removed and prematurely destroyed by macrophages in the spleen.
- These antibodies are produced by B-cells. Helper T-cells (CD4+) are also important in production of antibodies.
- Impaired platelet production also important in many cases. In adults, as many as 40% of ITP cases may have reduced platelet turnover reflecting inhibitory effect of platelet autoantibodies on megakaryopoiesis as well as due to cytotoxic T cell-mediated megakaryocytic damage.

Clinical Features

- There are two forms of ITP, an acute form that is more common in children and a chronic form that is more common in adults.
- Chronic ITP—persistence of thrombocytopenia for more than 6 months.
- Most cases are primary. Secondary ITP can occur in SLE and chronic infections like HIV and hepatitis C.

Acute ITP	Chronic ITP
• Most frequent in children (2–6 years)	• Most frequent in adults (20–40 years)
• Affects both sexes equally	• Females affected more than males (M:F ratio, 1:4)
• Commonly follows an antecedent upper respiratory viral infection	• Usually no preceding history of viral infection
• Usually a self-limiting disease	• Usually a chronic disease characterised by remissions and relapses
• Abrupt onset of haemorrhage into skin and mucous membranes—e.g. purpura, petechiae, ecchymoses, epistaxis, bleeding from oral cavity, gastrointestinal and genitourinary tracts	• Insidious onset of haemorrhage into skin and mucous membranes—e.g. purpura, petechiae, ecchymoses, epistaxis and menorrhagia. Purpurae are more common in the distal parts of limbs
• Intracranial haemorrhage occurs rarely	• Intracranial haemorrhage occurs very rarely

- Characteristically, the patient has no physical signs other than those due to bleeding and anaemia (occurs due to menorrhagia and epistaxis). Splenomegaly is characteristically absent in most patients (tip of spleen may be palpable in 10% case).
- May be associated with haemolysis (Evan's syndrome).
- More than two-third patients with acute ITP recover within 6 months. More than one-third of remaining patients recover in next few months to years.

Diagnosis

- Thrombocytopenia. Repeat platelet count using sodium citrate as anticoagulant so as to exclude pseudothrombocytopenia caused by platelet aggregation and clumping in the presence of EDTA anticoagulant.
- Positive tourniquet test (Hess test).
- Prolonged BT.
- Bone marrow examination characteristically shows normal or increased number and size of megakaryocytes. Bone marrow is not necessary in acute ITP with typical presentation if management involves observation or use of intravenous immunoglobulin or anti-RhD globulin.
- Antiplatelet antibodies may be demonstrated in blood. However, a negative test does not exclude ITP.
- In chronic ITP, exclude other causes like HIV, hepatitis C virus infection and lymphoproliferative disorders.

Treatment

- In acute and mild cases, no specific therapy will be necessary.
- Intervention is reserved for those who have overt haemorrhage and platelet counts below 20,000/mm^3 or those who have organ- or life-threatening bleeding irrespective of the circulating platelet count.
- Active bleeding should be treated with platelet concentrates.
- The main therapeutic measures are corticosteroids and splenectomy.
- Immunosuppressive therapy, intravenous immunoglobulin, anti-RhD globulin and thrombopoietin receptor agonists are indicated in selected cases.

Corticosteroids

- Indications of corticosteroids:
  - To induce remission.
  - Post-operatively, in failed splenectomy cases.
  - Pregnant females after the 5th month of pregnancy.
  - To maintain remission in chronic immune thrombocytopenic purpura.
- Dosage of corticosteroids:
  - Initial dose is 1–2 mg/kg of prednisolone/day.
  - Initial dose is continued for at least 2 weeks or if necessary 3–4 weeks, and then reduced slowly and stopped.

Splenectomy

- Indications of splenectomy:
  - Chronic cases, especially in adults who have not responded to corticosteroids.
  - Unacceptably high doses of corticosteroids in maintaining remission.
  - Emergency measure in children and adults, when there is severe bleeding or threatening cerebral haemorrhage (despite adequate corticosteroid therapy).
  - In the first 4–5 months of pregnancy, if steroids have failed to induce full remission.
- Mechanism of action of splenectomy:
  - Splenectomy removes the major site of platelet destruction.
  - Splenectomy brings down the concentration of circulating antiplatelet antibodies.

Immunosuppressive Therapy

- Agents used are vincristine, vinblastine, azathioprine, cyclophosphamide, cyclosporine and mycophenolate mofetil.
- Indications of immunosuppressive therapy:
  - Refractory cases (i.e. those who have failed to respond to corticosteroids and splenectomy).
  - Those in whom corticosteroid therapy and splenectomy are contra-indicated.

Intravenous Immunoglobulin

- Transient blockade of Fc receptors on macrophages in the reticuloendothelial system, especially the spleen, is believed to play a major role in the immediate, and often dramatic, platelet responses observed after intravenous immunoglobulin.
- Dose: 1–2 g/kg.
- Indications of intravenous immunoglobulin:
  - Acute situations prior to surgery and child birth, and in patients with intracranial bleed.
  - Those in whom corticosteroid therapy and splenectomy are contra-indicated.
  - Provides temporary effect only.
  - Often used prior to splenectomy as a temporising measure.
- Adverse effects include nausea, vomiting, fever and headache. Uncommon side effects include neutropenia and haemolytic anaemia.

Anti-RhD Globulin

- Effective in patients with ITP.
- Should be given only if the patient is Rh-positive.
- Useful in patients who do not respond to steroids and may be tried before splenectomy. The effect is usually temporary, and nearly 50–75% patients relapse over variable period.
- Proposed mechanism is coating of Rh(+) red blood cells by anti-RhD antibodies, which are then preferentially destroyed by the reticulo-endothelial cells with relative sparing of the antibody-coated platelets.
- Dose is 75 μg/kg intravenously.
- Side effects include nausea, vomiting, fever, chills and intravascular haemolysis.

Thrombopoietin (TPO) Receptor Agonists

- Two TPO-RAs for refractory ITP patients: eltrombopag and romiplostim.
- Eltrombopag is orally administered. Important adverse effects include deep vein thrombosis and embolism, and mild elevation in liver enzymes.
- Romiplostim is administered once a week subcutaneously.

Others

- Danazol, an androgen with low virilising activity has been tried in idiopathic thrombocytopenic purpura.
- Rituximab.

Emergency Treatment

- Required in case of life-threatening bleed.
- Intravenous administration of methylprednisolone (30 mg/kg, maximum dose 1 g) over 20 to 30 minutes plus platelet transfusion, followed by intravenous immunoglobulin (1 g/kg). Methylprednisolone is repeated daily for another 1–2 days.

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                                    │     ITP     │
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- Organ or life-threatening bleed (irrespective of platelet count)

- Platelet >30,000/mm³ without severe bleeding

- Platelet between 20,000 and 30,000/mm³ without severe bleeding

- Platelet <20,000/mm³ or serve bleeding tendency

- Platelet transfusion
- Intravenous Immunoglpbulin
- Intravenous methylprednisolone

- No treatment
- Regular follow-up

- Close observation

- Corticosteroids
- Splenectomy

Ineffective

- Immunosuppressive therapy
- Intravenous immunoglobulin
- Anti-RhD globulin
- Danazol
- Rituximab
- Thrombopoietin receptor agonists

Q. Discuss thrombotic thrombocytopenic purpura.

- Thrombotic microangiopathy (TMA) is the term for diseases in which disseminated microthrombi composed of agglutinated platelets occlude arterioles and capillaries. It includes thrombotic thrombocytopenic purpura and haemolytic uremic syndrome. Other conditions include disseminated intravascular coagulation, disseminated malignancy, malignant hypertension and microvascular vasculitis complicating autoimmune disorders such as systemic lupus erythematosus or certain infections such as Rocky Mountain spotted fever.
- Thrombotic thrombocytopenia purpura (TTP) is a severe microangiopathic haemolytic anaemia characterised by systemic platelet aggregation, organ ischaemia, profound thrombocytopenia (with increased marrow megakaryocytes) and fragmentation of erythrocytes.

Aetiology

- TTP is caused by a deficiency of ADAMTS-13, a metalloprotease that cleaves ultra-large von Willebrand (vWF) factor multimers into smaller, less adhesive multimers. Ultra-large vWF multimers cause extensive platelet aggregation and depletion of the circulating pool of platelets.
- Deficiency is often related to the presence of antibodies against this protease; rarely, it can be due to mutation in ADAMTS-13 gene (autosomal recessive).
- Several other causes can also produce deficiency of ADAMTS-13 and produce TTP.

- Medications (mitomycin C, cyclosporine, tacrolimus, quinidine, dipyridamole, ticlopidine, clopidogrel, gemcitabine, bevacizumab)
- Stem cell transplantation
- HIV infection
- Total body irradiation

- Pregnancy
- Autoimmune diseases
- Malignancy
- Idiopathic enzyme deficiency

Clinical Features

- The classic pentad of TTP is microangiopathic haemolytic anaemia with schistocytosis (at least 3 cells per 100), severe thrombocytopenia, fluctuating neurologic deficits secondary to central nervous system ischaemia, fever and renal abnormalities including haematuria and/or proteinuria.
- However, only a minority of patients have fever; renal involvement is also not required for the diagnosis.
- Neurologic features include headache, vertigo, confusion, seizures and focal deficits.

Diagnosis

- Presence of thrombocytopenia, schistocytes and elevated serum LDH (out of proportion to the degree of haemolysis) are sufficient to suggest the diagnosis of TTP. Elevated LDH also occurs due to release from ischaemic tissues.
- Normal PT, aPTT, fibrinogen and D-dimer are normal. Fibrin degradation products may be normal or slightly elevated.
- Red cells, red cell casts, and proteinuria on urine examination.
- Negative Coombs test.
- Reduced activity of ADAMTS-13 below 5–10% of normal.

Treatment

- Treatment of choice is daily plasma exchange (removing 40 mL/kg body weight of plasma and replacing it with equal volume of fresh frozen plasma). Continued for at least 2 days after remission (defined as stabilization of clinical symptoms and normalisation of platelet count and LDH levels along with rising haemoglobin). Plasma exchange removes ADAMTS-13 as well as ultra-large vWF multimers.
  - Plasma exchange should be initiated as soon as possible, preferably within 4–8 h, if a patient presents with a microangiopathic haemolytic anaemia and thrombocytopenia in the absence of any other identifiable clinical cause.
- Corticosteroids generally added to plasma exchange to suppress antibody production.
- Platelet transfusion of little value and probably contraindicated unless life-threatening bleeding occurs.
- Splenectomy in resistant cases. It removes antibody-producing cells.
- Rituximab, a monoclonal antibody against CD20, suppresses antibody-producing cells. Used in patients refractory to plasma exchange and corticosteroids. May also be used along with plasma exchange if CNS or heart are significantly involved.

Q. Discuss the clinical features, investigations and treatment of haemolytic-uraemic syndrome.

- More often, seen in children.
- Typical or diarrhoea-related haemolytic-uraemic syndrome (HUS):
  - Preceded by haemorrhagic enterocolitis that is caused by cytotoxin-producing serotypes of *Escherichia coli* (e.g. 0157:H7) or *Shigella dysenteriae* type 1. Shiga toxins-1 and 2, produced by enterohaemorrhagic *E. coli*, are the most frequent cause of diarrhoea-associated HUS. Recently new strain of Shiga producing *E. coli* (0104 : H4) has been reported from Europe.
  - Shiga toxins bind to globotriaosyl ceramide (GB3) membrane receptors present on endothelial cells of kidney and other target organs. This disrupts protein synthesis, causes endothelial cell death and damage, induces inflammatory and procoagulant cascades that promote microvascular thrombosis.
  - Usually occurs as a single episode, except in rare individuals who have a familial, recurrent type of the disease.
- Atypical or non-diarrhoea-related HUS:
  - More severe than typical type, and difficult to treat.
  - Can occur with diverse conditions, like pneumococcal infections, autoimmune disease, HIV, transplantation, irradiation and certain drugs (antiplatelet drugs, ticlopidine and clopidogrel, calcineurin inhibitors, cyclosporine and tacrolimus; chemotherapeutic agents, mitomycin C, cytosine arabinoside, and cisplatinum).

Clinical Features

- Most common in children between 1 and 5 years of age.
- Occurs within 2–12 days after initial episode of haemorrhagic enterocolitis.
- Classical presentation is with the triad of microangiopathic haemolytic anaemia, thrombocytopenia and renal failure.
- The commonest clinical presentation is acute pallor and oliguria, following diarrhoea or dysentery.
- Haematuria and hypertension common.

- Complications of fluid overload may result in pulmonary oedema and hypertensive encephalopathy. Despite thrombocytopenia, bleeding manifestations are rare.
- Neurological symptoms like irritability, encephalopathy and seizures may occur but are uncommon.

Investigations

- Anaemia, schistocytes on peripheral smear, elevate LDH and thrombocytopenia.
- Elevated blood urea and creatinine.
- Urine examination may show proteinuria and red blood cells.
- Normal PT and aPTT.
- Stool culture for enterohaemorrhagic *E. coli*; shiga toxin analysis in stools; PCR assay to detect shiga toxin genes in stool.

Treatment

- Therapy for diarrhoea-associated HUS is limited to supportive care for the renal and haematological complications.
- Antibiotics if shigellosis is suspected.
- Experimental: Eculizumab, monoclonal antibody to C5a, particularly in atypical HUS. A major risk is fulminant meningococcal infection. Meningococcal vaccination is mandatory, and the patients should take prophylactic antibiotics at least until 2 weeks after vaccination.

Q. What are the common causes of thrombocytosis?

- Thrombocytosis indicates a platelet count $>450 \times 10^3/mm^3$.

Causes

- Iron deficiency anaemia - Acute or chronic blood loss - Post-surgery - Malignancy (paraneoplastic feature) - Infections - Rebound after correction of vitamin B_{12} or folate deficiency - Haemolysis **Tissue inflammation** - Collagen vascular disease (e.g. rheumatoid arthritis) - Inflammatory bowel disease	**Post-splenectomy or hyposplenism** **Myelodysplastic disorders** - Idiopathic sideroblastic anaemia **Myeloproliferative neoplasms** - Polycythaemia vera - Idiopathic myelofibrosis - Essential thrombocytosis - Chronic myeloid leukaemia

Q. Discuss the aetiology, classification, clinical features, diagnosis and management of haemophilia A.

Q. Write a short note on acquired haemophilia A.

Aetiology

- Haemophilia A is an X-linked genetic disorder of coagulation, affecting males. It results from a reduction of factor VIII (antihaemophilic factor).
- Antihaemophilic factor (factor VIII) is primarily synthesised by the liver. Plasma factor VIII has a half-life of 12 hours. In the plasma, it is carried bound to the von Willebrand's factor (vWF).
- Incidence of haemophilia A is 1 in 10,000 males.
- Acquired haemophilia A occurs due to presence of inhibitors (antibodies) against factor VIII and is unrelated to presence of congenital haemophilia A. It is more common in elderly patients. In about 50% cases, no underlying disease

is present while in others, acquired hameophilia A is associated with autoimmune disorders, malignancies, pregnancy, various drugs (e.g. penicillin, sulphonamides, phenytoin), and dermatological diseases. Presentation is with acute onset of severe, and life-threatening bleeding. Spontaneous subcutaneous, deep muscle and retroperitoneal bleeds represent the majority of events, but gastrointestinal, pulmonary and intracranial bleeds also occur. Trauma-related muscle bleeds and haemarthroses are uncommon.

Genetics

- Haemophilia A is an X-linked recessive disorder.
- A haemophilic patient's daughters will all be carriers, but all his sons will be normal. A carrier female has a 50% chance of producing a haemophilic male or a female carrier.
- Females can be haemophilic if:
  - She is born to an affected father and a carrier mother (25% risk).
  - She has Turner's syndrome (45 XO).
  - She has inactivation of normal X-chromosome due to lyonization (rare).
- The degree of factor VIII deficiency and severity of bleeding tend to be similar in all the affected members of the same family.

Classification

- Normal factor VIII level in the blood is 0.50–1.50 IU/mL. Haemophilia A can be classified based on the factor VIII activity in blood.

- Severe less than 1% of normal activity
- Moderate 1–5% of normal activity
- Mild more than 5% of normal activity

Clinical Features

- Haemophilia A is characterised by excessive bleeding. Virtually, no tissue is exempted from this. Spontaneous bleeding usually occurs after 6 months of age but in severe cases, it can occur in the first month also.
- When bleeding follows trauma, it is characteristically "delayed".
- Bleeding tendency may range from mild to severe.

Bleeding into Joints (haemarthroses)

- Recurrent bleeding into large joints, especially knees, elbows, ankles, wrists and hips.
- Bleeding usually spontaneous or following minor trauma.
- In the acute stage, the affected joint is swollen, hot, tender and movements severely restricted. All these gradually subside over a period of days.
- Repeated haemarthroses eventually result in deformity, crippling and disuse atrophy of muscles around the joint.

Bleeding into Muscles

- Muscle haematomas are common in calf and psoas muscles.
- Psoas haematomas may compress the femoral nerve resulting in sensory disturbances over thigh and quadriceps weakness. Often the patient is left with some residual weakness in the leg.
- Calf haematomas can result in contraction and shortening of the Achilles tendon.

Other Bleeding Manifestations

- Bleeding from wounds.
- Bleeding from sockets after dental extraction.
- Easy bruising.
- Retroperitoneal, mesenteric and intra-abdominal bleeding.
- Bleeding into muscles of tongue.
- Intracranial haemorrhage (subdural haematoma and intracerebral haemorrhage).
- Haematuria and ureteric colic due to passage of blood clots.

Investigations

- BT, PT and platelet counts are normal.
- Activated partial thromboplastin time (aPTT) is typically prolonged.
- Specific factor VIII assay can confirm the diagnosis.

Antenatal Diagnosis

- Chorion villous sampling (CVS) at 8–9 weeks' gestation, sexing the foetus and using informative factor VIII probes.
- Sexing the foetus at 16 weeks' gestation by amniocentesis and, if male, a foetal blood sampling at about 19–20 weeks.
- The first technique is preferable than the second.

Management

- Routine immunisations, such as diphtheria-tetanus-pertussis or measles-mumps-rubella should be given subcutaneously using a thin needle.
- Given the risk of exposure to blood-derived products, patients should be vaccinated against hepatitis B by giving vaccine subcutaenously.

Local Treatment

Wounds and Mucous Membrane Bleeding

- Local pressure may be applied digitally, with pressure bandages or sutures.
- Topical haemostatics like adrenaline and thrombin.
- Immobilisation of wounds by bandages, splinting, etc.

Haematomas and Haemarthrosis

- In acute stage, elevation of the affected part and immobilisation by splinting and bandages should be used. Pain is relieved by analgesics like acetaminophen or codeine. Drugs like aspirin affecting platelet function are contraindicated.
- Once acute stage is over, patient should be mobilised and should receive physiotherapy.

Replacement Therapy

- Replacement therapy is aimed at rapid correction of deficiency of factor VIII.
- Agents currently used for replacement therapy are cryoprecipitate and factor VIII concentrate given intravenously.
- Indications of replacement therapy:
  - Early treatment of spontaneous bleeding episodes.
  - Established severe or prolonged wound and tissue bleeding.
  - Control of bleeding during and after surgery and trauma.
- Prophylactic infusion (once every 2–3 days) is recommended at present in all patients with severe haemophilia so as to prevent arthropathy. Prophylaxis is superior to on-demand therapy in delaying or preventing the development of haemophilic arthropathy.
- One unit of factor VIII is that amount present in 1 mL of normal plasma. An individual with a plasma volume of 3000 mL would have 3000 units of clotting factor in the circulation. Each unit of cryoprecipitate contains about 100 units of factor VIII.
- Calculation of dose: For factor VIII, 1 unit/kg will raise blood level by 2%. In major bleeds, the aim is to raise factor VIII levels to at least 50% (presuming the initial level to be 0). This is maintained for 3–5 days. Volume of distribution for factor VIII is approximately 0.5 (i.e. half the plasma volume). The calculated dose is administered twice a day. The dose is calculated as:

$$\text{Dose of factor VIII} = \text{Desired factor level (\%)} \times \text{Weight (kg)} \times 0.5$$

- Complications of replacement therapy:
  - Transmission of infections (e.g. hepatitis B virus, delta virus, hepatitis C virus, HIV infection).
  - Development of anti-factor VIII antibodies.

Desmopressin

- Causes release of stored vWF and factor VIII from endothelial cells into plasma.
- Desmopressin (DDAVP; 1-desamino-8-D-arginine vasopressin) can transiently raise factor VIII activities by 3–5 times. It is given intravenously at a dose is 0.3 mcg/kg over 15 minutes. Intranasal route can be used for oral bleeding and before dental procedures. Patients should be advised to limit water intake to reduce chances of hyponatraemia.
- Indications are minor bleeding and minor surgery.

Epsilon Amino-Caproic Acid (EACA) and Tranexamic Acid

- These are antifibrinolytic agents that exert their effect by inhibiting the proteolytic activity of plasmin and, therefore, inhibiting fibrinolysis.
- When used concurrently with replacement therapy, these agents can reduce the factor VIII requirements.
- Indicated for control of oral and nasal bleeding, and menstruation.
- Commonly used for dental extractions. Regimen is EACA taken orally in a dose of 5 g four times daily for 7 days, starting on the day of extraction. For tranexamic acid, dose is 10 mg/kg intravenously (or 15–25 mg/kg orally) 6-8 hourly.
- Contraindicated in presence of haematuria because of increased risk for intrarenal or ureteral thrombosis, and in presence of DIC or thromboembolic disease.

Treatment for Patients with Inhibitors against Factors

- Use of bypassing agents such as recombinant factor VIIa or activated prothrombin complex concentrates.
- Eradication of the inhibitor by means of immune tolerance induction:
  - Patients receive repetitive doses of factor VIII (or factor IX in haemophilia B), usually once a day, with or without associated immunosuppressive (immune tolerance therapy).
  - Typically, there is an initial rise in antibody titres as a result of anamnestic response.
  - Subsequently, however, a gradual reduction in titre is seen until in the end, the inhibitor becomes undetectable.
  - After successful immune tolerance, patients continue on regular factor infusions.
- Use of immunosuppressive agents (e.g. steroids, cyclophosphamide, rituximab).

Q. Briefly discuss haemophilia B (Christmas disease) and its management.

- It is an X-linked disorder resulting in deficiency of factor IX.
- Clinical features are indistinguishable from haemophilia A. Patients with severe disease present with muscle haematomas and haemarthroses progressing to crippling joint deformities.
- Diagnosis is established by factor IX assay.

Management

- Management is similar to that of haemophilia A.
- Desmopressin is not effective.
- Replacement therapy:
  - Fresh frozen plasma is used to treat mild to moderate bleeding.
  - Factor IX concentrate (prothrombin complex concentrates) is used to treat moderate to severe bleeding. Presently available factor IX concentrates are a mixture of factor II, VII, IX and X, and protein C and S. Hence, the replacement therapy carries an additional risk of thromboembolism.

Q. Discuss the aetiology, clinical features, investigations and treatment of von Willebrand's disease.

- Most common inherited bleeding disorder.
- von Willebrand's disease (vWD) is characterised by the deficiency or dysfunction of von Willebrand factor (vWF).
- There are three major types of vWD: type 1 (partial quantitative deficiency), type 2 (qualitative defect—type 2A, 2B, 2M and 2N) and type 3 (complete absence of vWF).
- Type 2N and type 3 are inherited as autosomal recessive. Type 2A and 2M are usually autosomal dominant though a few cases may be autosomal recessive. Type 1 is autosomal dominant.

von Willebrand Factor

- It is a protein synthesised by endothelial cells and megakaryocytes. It has two main functions:
  - von Willebrand factor acts as a carrier protein for factor VIII. A deficiency of vWF hence causes a secondary reduction of factor VIII leading to a coagulation defect.
  - von Willebrand factor plays an important role in platelet adhesion by forming bridges between platelets and subendothelial tissue. Hence, the deficiency of vWF results in a defect of platelet function.

Clinical Features

- Clinical presentation can be very variable, ranging from a severe haemorrhagic disorder to an asymptomatic condition.
- Common clinical manifestations are epistaxis, easy bruising, menorrhagia, post-partum haemorrhage and haemorrhage following trauma, surgery and dental extraction.
- Less common clinical manifestations are haematuria, gastrointestinal bleeding and haemarthrosis.

Investigations

- Prolongation of BT and aPTT, particularly in type 3 vWD.
- The initial tests commonly used to detect vWD are determinations of plasma levels of vWF antigen (vWF:Ag), vWF function by von Willebrand ristocetin cofactor assay (vWF:RCo) and factor VIII assay.
  - vWF: Ag is an immunoassay that measures the concentration of vWF protein in plasma.
  - The most specific diagnostic method is Ristocetin cofactor test that shows a reduction in biologic activity in the form of interaction with platelets. The antibiotic Ristocetin causes vWF to bind to platelets via GP1b, resulting in platelet clumps and their removal from the circulation.
  - Factor VIII coagulant assay is a measure of the cofactor function of factor FVIII in plasma.
  - Remember, vWF is also an acute-phase reactant and plasma levels may be high in conditions of stress, inflammation, exercise, and pregnancy.

Management

- Mild bleeding is managed with desmopressin.
- Severe bleeding can be controlled by intravenous cryoprecipitate.
- Use of plasma-derived concentrates containing vWF and factor VIII is recommended in place of cryoprecipitate as the former are virus inactivated.
- For oral surgical procedures, EACA is given orally in a dose of 5 g four times daily for 7 days, starting on the day of procedure.
- Menorrhagia is managed with hormonal suppression.

Q. Write briefly on recombinant factor VII activated.

- Recombinant factor VII activated (factor VIIa) is approved for management of patients with congenital factor VII deficiency and haemophilia A or B with inhibitors:
  - presenting with episodes of severe haemorrhage or
  - during peri-operative management of bleeding.
- Several other conditions where factor VIIa may be of use:
  - Trauma with massive bleeding.
  - Intracranial bleeding.
- Important complications include venous and arterial thrombosis.

Q. Discuss the causes, pathogenesis, clinical features, lab features and management of disseminated intravascular coagulation (DIC; defibrination syndrome; consumption coagulopathy).

- Disseminated intravascular coagulation (DIC) is an acute or chronic bleeding disorder due to intravascular activation of coagulation and is caused by a variety of conditions.
- Diffuse intravascular clotting results in utilisation (consumption) of coagulation factors V, VIII and fibrinogen, and platelets, which in turn leads to bleeding. The cardinal clinical manifestations of DIC are bleeding and organ damage.

Causes

Acute

Infections:
- Septicaemia
- Gram-negative infections
- Meningococcal infections
- Malaria
- Fungal infections

Obstetric:
- Abortions
- Septicaemia
- Pre-eclampsia/eclampsia
- Retained dead foetus
- Amniotic fluid embolism
- Acute fatty liver of pregnancy

Others:
- Snake bite
- Major surgery or trauma
- Heat stroke
- Neoplasms especially chronic promyelocytic leukaemia
- Cancer chemotherapy
- Tumour lysis syndrome
- Shock
- Haemolytic transfusion reaction
- Acute transplant rejection
- Fat embolism
- Near drowning
- Aortic aneurysm
- Shock
- Acute pancreatitis
- Catastrophic antiphospholipid syndrome

Chronic
- Malignancies
- Abruptio placentae
- Giant haemangioma (Kasabach-Merritt syndrome)

Pathogenesis and Clinical Features

Triggering mechanism (e.g. tissue factor, endotoxins)

Activation of coagulation cascade

Disseminated intravascular coagulation (DIC) with fibrin deposition in microvasculature

Secondary fibrinolysis

Consumption of platelets and coagulation factors

Organ damage
Brain
Kidney – renal failure
Gangrene of digits, genitalia and nose

Hypotension

Bleeding manifestations
Skin and mucous membrane
Operation sites
Venepuncture sites
Gastrointestinal bleeding
Haematuria
Uterine bleeding

- There is a spectrum of thrombosis and haemorrhage in all cases of DIC; each or both may be encountered. Most cases present with haemorrhage.
- In sepsis-induced DIC, bleeding manifestations are more common than thrombosis.
- Purpura fulminans—characteristic thrombotic manifestation of sepsis.
- Waterhouse–Friderichsen syndrome—an occult thrombosis of adrenal vein thrombosis resulting in adrenal haemorrhage.
- In cancers, chronic DIC may lead to hypercoagulability. Migratory venous thrombosis is known as Trousseau sign.

- Multiorgan dysfunction syndrome (MODS) is a frequent consequence of DIC and is usually due to bleeding into organs or thrombotic alterations in various organs (hepatic, cardiac, central nervous, renal and pulmonary systems).

Chronic DIC

- A compensated state that develops when blood is continuously or intermittently exposed to small amounts of tissue thromboplastin.
- There may be little obvious clinical or laboratory indication of the presence of DIC.

Investigations

- Low erythrocyte sedimentation rate (ESR) due to reduced fibrinogen.
- Thrombocytopenia.
- Prolongation of PT and activated partial thromboplastin time (aPTT). However, these tests may be normal in more than 40% cases; this is due to presence of circulating activated clotting factors, such as thrombin or Xa, which can accelerate the formation of thrombin.
- Reduced plasma fibrinogen level that correlates most closely with bleeding. However, fibrinogen is an acute phase reactant, and patients with conditions that cause elevation in acute phase reactants (e.g. inflammation, sepsis) may have normal serum values of fibrinogen. Further, in chronic DIC, fibrinogen and platelets may be normal.
- Elevated levels of fibrin degradation products (FDPs).
- D-dimer (formed during fibrinolysis as a result of degradation of cross-linked fibrin by plasmin) levels are elevated in almost all cases of DIC. However, it is important to remember that many conditions other than DIC, such as trauma, recent surgery or venous thromboembolism, are associated with elevated FDPs including D-dimer. Also, because FDPs are metabolised by the liver and secreted by the kidneys, liver and kidney impairment can influence their levels.
- Schistocytes on peripheral smear.

Management

- Elimination of underlying causes—e.g. removal of a dead foetus, placenta, etc.
- Correction of precipitating factors like acidosis, dehydration and hypoxia.
- Replacement of coagulation factors and platelets by fresh whole blood, fresh frozen plasma, cryoprecipitate, and platelet concentrates. It is indicated in patients with active bleeding, in those requiring an invasive procedure and those who are otherwise at risk for bleeding complications. Severe hypofibrinogenaemia that persists despite FFP replacement may be treated with fibrinogen concentrate or cryoprecipitate.
- Dose:
  - Cryoprecipitate – 1 unit/10 kg.
  - Fresh frozen plasma – 15–20 mL/kg.
  - Platelet concentrates – 1–2 units/10 kg.
- Target is to achieve:
  - Fibrinogen level 100–150 mg/dL.
  - Platelets >50,000/mm^3.
  - Haemoglobin 6–10 g/dL.
  - Prothrombin time and activated partial thromboplastin time of less than 1.5 times the control.
- Inhibition of coagulation process:
  - Role of heparin is controversial. However, it is often given in patients with thrombotic manifestations (e.g. arterial or venous thromboembolism, severe purpura fulminans associated with acral ischaemia or vascular skin infarct). Average requirement is 1000 units/hour by continuous intravenous infusion. It should be given after the correction of bleeding risk. Major indications of heparin are:
    - Platelet counts or coagulation factors do not increase following replacement and patient continues to bleed.
    - Retained dead foetus (before induction of labour).
    - Deposition of fibrin resulting in purpura fulminans or venous thromboembolism.
    - In acute promyelocytic leukaemia, before induction chemotherapy (to prevent DIC).
  - In critically ill, non-bleeding patients with DIC, prophylaxis for venous thromboembolism with prophylactic doses of heparin or low-molecular weight heparin is recommended.

- Antifibrinolytic agents (tranexamic acid and epsilon aminocaproic acid) are contraindicated as they may cause enhanced precipitation of fibrin in microcirculation and macrocirculation and lead to fatal disseminated thrombosis.

Q. Give a brief account of vitamin K.

- Vitamin K is a fat-soluble vitamin and it exists in two forms:
  - Vitamin K_1 (phylloquinone) is present in vegetable oils and green leafy vegetables.
  - Vitamin K_2 (menaquinone) is synthesised by colonic bacteria.
- Vitamin K_3 (menadione) is a synthetic pro-vitamin that can be converted to menaquinone by the liver. It is available in injection form for therapeutic use.
- Vitamin K is necessary for the post-translational carboxylation of some coagulation factors synthesised in the liver. This is necessary for the functioning of these factors. These factors include factor II, VII, IX and X; protein C and protein S. Warfarin-type anticoagulants inhibit carboxylation by preventing the conversion of vitamin K to its active hydroquinone form.
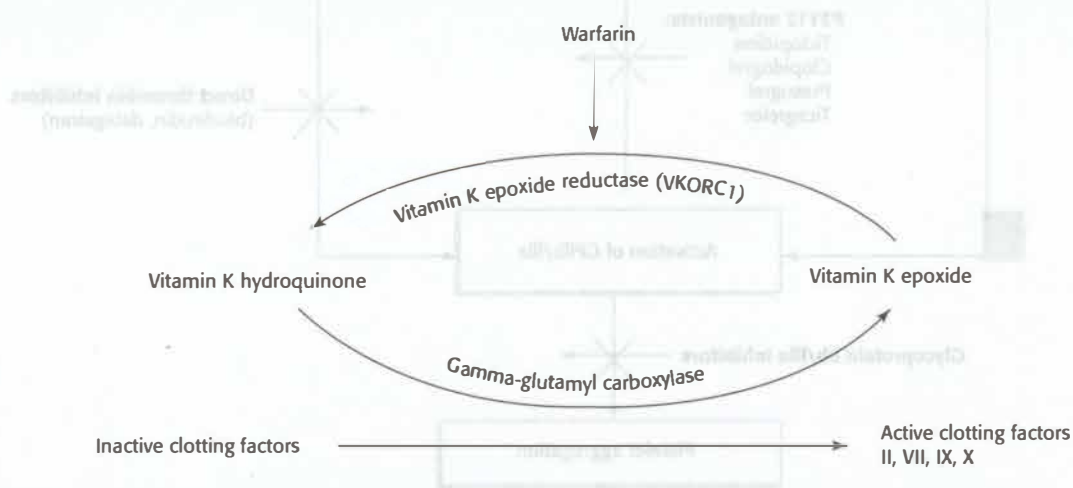
- Vitamin K deficiency occurs with diseases that interfere with fat absorption, long-term antibiotic therapy and warfarin therapy.
- Deficiency manifests as haemorrhagic stage.
- Deficiency is treated with daily injections of 10 mg of vitamin K. Vitamin K may not be effective in the presence of liver cell disease.

Q. Give a brief account of antiplatelet drugs.

- Prevent and/or reverse platelet aggregation in arterial thrombosis and inhibit thrombin formation. These are classified below:

Classification

Cyclooxygenase inhibitor	Adenosine reuptake inhibitor
• Aspirin	• Dipyridamole
Adenosine diphosphate (ADP) receptor inhibitors (thienopyridines)	**Glycoprotein IIb/IIIa inhibitors**
• Ticlopidine	• Abciximab
• Clopidogrel	• Eptifibate
• Prasugrel	• Tirofiban
• Ticagrelor	

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                    ┌─────────────────────┐
                    │   Ruptured plaque   │
                    └──────────┬──────────┘
                               │
                               ▼
                    ┌─────────────────────┐
                    │  Platelet activation │
                    └──────────┬──────────┘
   Aspirin ──✕──▶
                    ┌──────────────┐  ┌──────┐  ┌──────────┐
                    │ Thromboxane A₂│  │ ADP  │  │ Thrombin │
                    └──────────────┘  └──────┘  └──────────┘
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P2Y12 antagonists:
Ticlopidine
Clopidogrel
Prasugrel
Ticagrelor

Direct thrombin inhibitors
(bivalirudin, dabigatran)

Activation of GPIIb/IIIa

Glycoprotein IIb/IIIa inhibitors ──✕──▶

Platelet aggregation
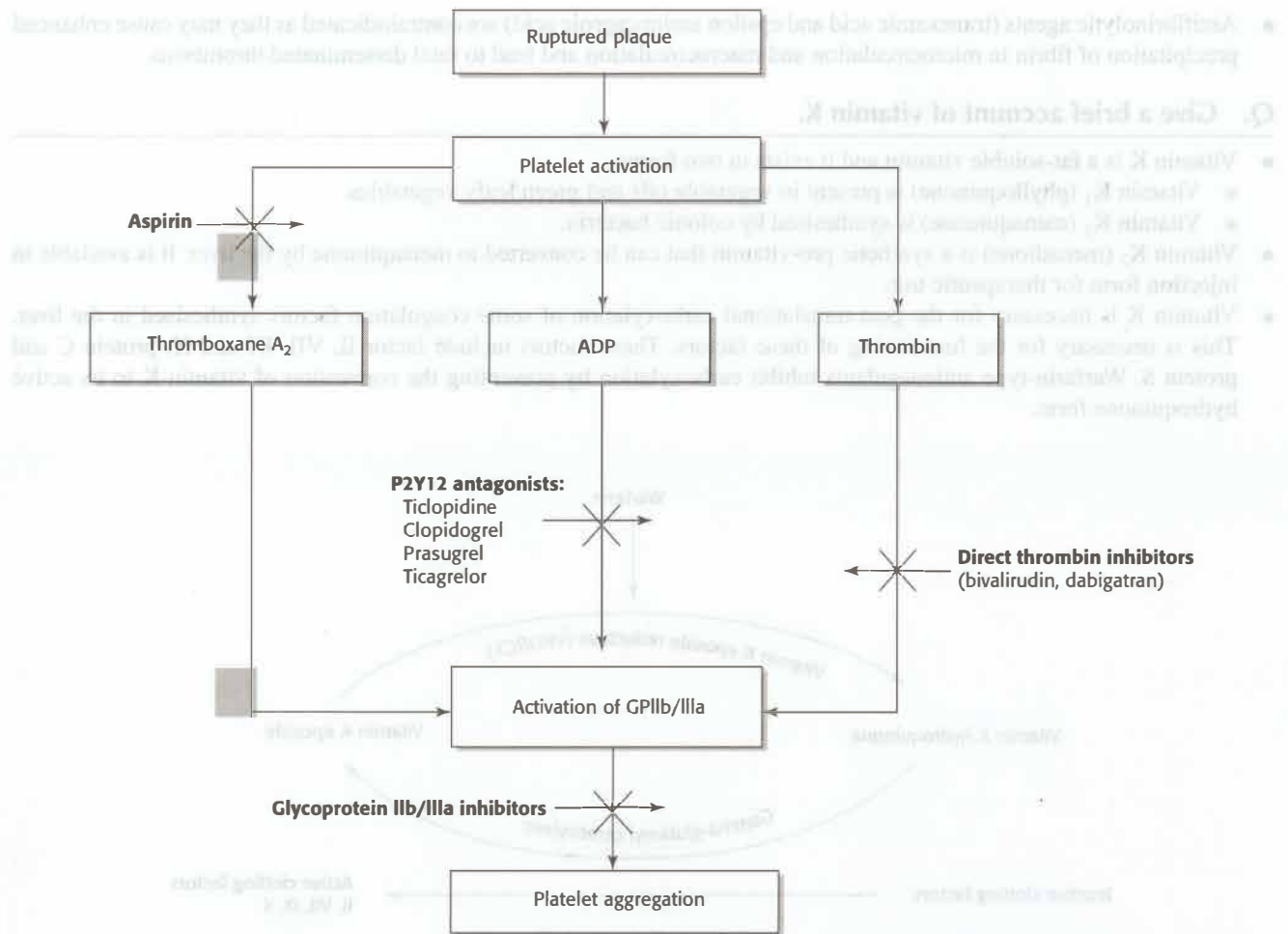
Cyclooxygenase Inhibitors

- Aspirin inhibits cyclooxygenase (both COX-1 and COX-2) that leads to prevention of synthesis of thromboxane A2 and impairment of platelet secretion and aggregation.
- Effects of aspirin on platelet function occur within an hour and last for the whole lifespan of platelets (7 days).
- Though the antiplatelet effects are seen with a low dose of 50 mg/day, the usual dose is 75–325 mg/day.
- Useful in acute coronary syndromes, stable angina, transient ischaemic attack, stroke following carotid artery surgery, atrial fibrillation (to prevent thrombosis) and intermittent claudication.
- Important side effects are upper GI bleed and renal function impairment.

Adenosine Reuptake Inhibitors

- Dipyridamole inhibits the cellular reuptake of adenosine into platelets leading to increased extracellular concentrations of adenosine. Adenosine interacts with the adenosine receptors to cause increased cAMP via cyclic adenylate cyclase. cAMP impairs platelet aggregation and also causes arteriolar smooth muscle relaxation.
- Used in coronary artery disease, cerebral ischaemia and in nuclear cardiac stress testing (where it acts as coronary vasodilator).
- Dose is 25–75 mg three to four times a day.
- Side effects include allergic reactions, vomiting, dizziness and headache. Due to vasodilatory property, it can lower the blood pressure.
- Rarely used at present due to dose inconvenience and side effects.

Adenosine Diphosphate Receptor Antagonists (Thienopyridines) or P2Y₁₂ Antagonists

- ADP, an important platelet agonist, has two types of receptors in the platelet plasma membrane: $P2Y_1$ and $P2Y_{12}$. $P2Y_{12}$ is a 7-transmembrane domain receptor linked to a G inhibitory protein. The end result of ADP signaling through its $P2Y_{12}$ receptor is an amplification of stable platelet aggregation and secretion.

- P2Y$_{12}$ ADP antagonists include ticlopidine, clopidogrel, prasugrel and ticagrelor that inhibit binding of ADP to platelet receptor P2Y$_{12}$, thereby inhibiting activation of the glycoprotein (GP) IIb/IIIa complex and platelet aggregation.
- One of the serious adverse effects of ticlopidine is occurrence of TTP. This side effect is less common with clopidogrel.
- With clopidogrel, inhibition of platelet aggregation occurs within 2 hours after an oral dose of 300 mg. In patients with acute coronary syndrome, 600 mg loading dose is recommended in patients who will undergo angiography and possible revascularisation within 24 hours of diagnosis. If angiography is not planned, loading dose is 300 mg. The usual daily dose is 75 mg. The platelet functions return to normal about 7 days after the last dose. This can lead to bleeding problems when surgery particularly CABG surgery is done in patients on the drug. Clopidogrel needs to be discontinued at least 5 days before any major surgery. About one-third of patients on clopidogrel are resistant and show only a low level of platelet inhibition.
- Prasugrel has a more rapid onset of action with its duration of action longer than that of clopidogrel. It is able to achieve higher degrees of platelet inhibition than clopidogrel. A loading dose of 60 mg prasugrel is generally recommended after angiography. Maintenance dose of prasugrel is 10 mg daily. Risk of bleeding is higher compared to clopidogrel.
- Ticagrelor differs from clopidogrel and prasugrel in that it binds reversibly rather than irreversibly to P2Y$_{12}$ platelet receptor and has a more rapid onset but of shorter duration of action than clopidogrel.
- Where fibrinolytic therapy is planned for ST-elevation myocardial infarction, a 300 mg loading dose of clopidogrel should be used and prasugrel and ticagrelor avoided. In patients with ACS with planned revascularisation, aspirin can be combined with clopidogrel (600 mg loading dose), prasugrel (60 mg loading dose) or ticagrelor (180 mg loading dose).

Glycoprotein IIb/IIIa Inhibitors

- This category includes abciximab, eptifibatide and tirofiban.
- Used in the setting of percutaneous coronary interventions, unstable angina and non-ST-elevation MI.
- Abciximab is a chimeric monoclonal Fab fragment of murine and human immunoglobulin that binds to GPIIb/IIIa.
- Given by intravenous route.
- Side effects include bleeding tendencies and thrombocytopenia. Eptifibate may also produce hypotension.

Q. Classify anticoagulants. Give a brief account of the commonly used anticoagulants.

Classification

- Rapidly acting (parenteral)—e.g. heparin (unfractionated and low-molecular weight heparins), hirudins, heparinoids, indirect factor Xa inhibitors (fondaparinux and idraparinux), direct factor Xa inhibitors (apixaban, rivaroxaban).
- Slow acting (oral):
  - Coumarin derivatives—e.g. warfarin sodium, dicoumarol. These are most commonly used.
  - Indandione derivatives—e.g. phenindione, diphenindione (not used clinically).
  - Direct thrombin inhibitors—e.g. dabigatran.

Anticoagulant Therapy

- When anticoagulation is required on an urgent basis and for long term, therapy is initiated with heparin along with oral anticoagulants which is followed by oral anticoagulants alone—for example, in the following clinical situations:
  - Atrial fibrillation and cardiac disorders with thromboembolism.
  - Deep venous thrombosis (DVT).
  - Cerebral venous thrombosis.
  - Stroke in evolution and resistant transient ischaemic attacks.
  - Pulmonary thromboembolism.
  - Unstable angina and non-ST-elevation myocardial infarction.
  - Prosthetic valves.
  - Delayed initiation in cardiac thromboembolic disorders.
- When anticoagulation is needed for only brief periods, heparin alone is used—for example, in the following clinical situations:
  - Cardiac bypass surgery.
  - Haemodialysis.
  - DIC.

Unfractionated Heparin

- Heparin acts by binding to antithrombin, thereby potentiating its action. Though antithrombin complexes with and inhibits all activated clotting factors (except factor VIIa), its predominant action is to inhibit activated factor IIa (thrombin).
- Conventional heparin preparations are heterogeneous and unfractionated, with only 20% of the product biologically active. In addition, active heparin fractions may vary considerably in molecular weight.
- Heparin is given as an initial loading dose of 80–100 units/kg intravenously, followed by maintenance. For maintenance, any one of the following three regimens may be used:
  - Continuous intravenous.
  - Intermittent intravenous.
  - Intermittent subcutaneous.
- For total anticoagulation, continuous intravenous maintenance is preferred. Here, heparin is administered using an infusion pump at a rate of 18 units/kg/hour.
- For low-dose heparinisation (e.g. prophylaxis of DVT), 5000 units 12 hourly or 8 hourly subcutaneously are preferred.
- Duration of therapy is variable, but is usually 7–10 days. Overlapping therapy with warfarin should be started along with heparin.
- Heparin therapy is monitored with activated partial thromboplastin time (aPTT), which is maintained at 1.5–2 times the control value.
- Antidote of heparin is protamine sulphate. Fresh frozen plasma has little effect on bleeding associated with heparin, low-molecular weight heparins and fondaparinux.
- Complications of heparin therapy include bleeding, thrombocytopenia, skin necrosis, osteoporosis and osteomalacia (in long-standing therapy). Heparin-induced thrombocytopenia (HIT) is of two types: HIT type I and HIT type II.
  - HIT type I is a benign form that often resolves despite continued heparin therapy.
  - HIT type II (also known as HIT) is due to platelet-activating IgG antibodies that recognise complexes of platelet factor IV bound to heparin, leading to activation of platelets, thrombocytopenia, and risk of thrombosis. It presents 5–14 days after heparin exposure with thrombotic features (HIT and thrombosis syndrome). Can occur with all types of heparin.

Diagnostic Criteria for HIT Type II

Clinical
- At least one of the following:
  - Thrombocytopenia
  - Thrombosis (e.g. deep vein thrombosis, pulmonary embolism, adrenal haemorrhage, cerebral vein thrombosis, splanchnic vein thrombosis, limb artery thrombosis, stroke, myocardial infarction, mesenteric artery thrombosis)
  - Necrotising skin lesions at heparin injection sites
  - Acute anaphylactoid reaction (Usually occurs 5–30 minutes after intravenous heparin bolus; rarely, after subcutaneous heparin)

Timing
- Above events bear temporal relation to a preceding heparin exposure

Pathologic
- Heparin-dependent, platelet-activating IgG:
  - Positive platelet activation assay (e.g. serotonin-release assay)
  - Positive anti-PF4/polyanion-IgG EIA

Treatment of HIT Type II

- Immediately stop all types of heparins including "flushes" of heparin.
- Do not give warfarin as it can lead to venous limb gangrene or classic skin necrosis. Vitamin K is recommended if a diagnosis of HIT is made after warfarin has already been started.
- Start non-heparin anticoagulants (lepirudin–a recombinant hirudin, argatroban, danaparoid, fondaparinux and bivalirudin).
- Do not transfuse platelets even though severe thrombocytopenia is present.

Low-Molecular Weight Heparins (LMWH)

- These are biologically active forms of conventional heparin with molecular weights ranging from 3000 to 8000 Daltons.
- LMW heparins exert their anticoagulant effect primarily by inhibiting activated factor X (Xa) rather than activated factor II (IIa), which is preferentially inhibited by unfractionated heparin. Factor Xa inhibition is through binding to antithrombin.
- They have several advantages:
  - They can be administered subcutaneously once or twice a day.
  - Their pharmacokinetics is so predictable that aPTT monitoring is not necessary.
  - They are less immunogenic and are less likely to cause thrombocytopenia.
  - Many patients with deep vein thrombosis can be treated on an outpatient basis.
  - The main disadvantage is their cost.
- Commonly available LMWH include enoxaparin, dalteparin and tinzaparin.

Warfarin

- Warfarin acts by inducing a state analogous to vitamin K deficiency.
- Vitamin K is necessary for the post-translational carboxylation of some coagulation factors synthesised in the liver. This is necessary for the functioning of these factors. These factors include factor II, VII, IX and X; protein C and protein S. Warfarin-type anticoagulants inhibit carboxylation by preventing the conversion of vitamin K to its active hydroquinone form.
- When short-term heparin followed by long-term warfarin is used, both anticoagulants must be started simultaneously.
- Heparin should be continued for a minimum of 4 days because the peak antithrombotic effect of warfarin is delayed for about 96 hours, independently of PT. The PT is particularly sensitive to factor VII deficiency. Factor VII has a short half life of only 4–6 hours, and therefore, PT may get prolonged within a day of administration of warfarin. The goal is to inhibit all vitamin K-dependent factors; factor X and prothrombin have half-lives of less than 2 days.
- Along with warfarin, initial bridging therapy with heparins is necessary to avoid a potential hypercoagulable state induced by warfarin's effect on protein C, which has a short half-life of approximately 6 hours.
- Warfarin is started with an initial dose of 5 mg orally on the first day. Subsequent daily doses are adjusted according to PT, which is maintained at 1.5–3 times the control value. Usual maintenance dose varies from 2.5 to 7.5 mg/day.
- Duration of therapy is variable ranging from 3 months to lifelong.
- Many drugs can interfere with warfarin therapy. This should be monitored by checking PT before and after stopping any other drug.
- Complications of warfarin therapy are bleeding and haemorrhagic skin necrosis. Venous limb gangrene can occur as a complication of warfarin therapy if an underlying hypercoagulable state (e.g. HIT type 2) is present (although it can also occur without underlying HIT). The pathogenesis of skin necrosis and venous limb gangrene involves microthrombosis formation due to depletion of protein C in the setting of increased thrombin generation (e.g. from HIT). Skin necrosis involves skin and subcutaneous tissues at central (non-acral) sites, for example, breast, abdomen, thigh and calf. In contrast, in venous limb gangrene, acral (distal) necrosis occurs in the affected limb. International normalised ratio (INR) is markedly elevated due to depletion of protein C.
- Antidotes of warfarin are injections of vitamin K1, 5 mg intravenously or fresh frozen plasma or prothrombin complex concentrate. Prothrombin complex concentrate is a human-derived blood product containing the vitamin K–dependent clotting factors (II, VII, IX, X, protein C and protein S) and heparin. This product is therefore contraindicated in patients with HIT.
- Contraindications:
  - Severe uncontrolled hypertension.
  - Severe renal or liver failure.
  - Pre-existing haemostatic disorders.
  - Pregnancy.

International Normalised Ratio

- Thromboplastic reagents used for prothrombin test are derived from a variety of sources and give different PT results for the same plasma.
- Therefore, each thromboplastin is compared with an international reference preparation so that it can be assigned an international sensitivity index (ISI).
- INR is calculated as the ratio of the patient's PT to the mean PT for a group of normal people and then adjusted for ISI.

Limitations of Warfarin and Related Drugs

Limitation	Consequences
• Slow onset of action	• Need of overlapping with heparin
• Genetic variation in metabolism	• Variable dose required in different patients
• Multiple drug and food interactions	• Frequent monitoring by INR
• Narrow therapeutic index	• Frequent monitoring by INR

Hirudin

- Hirudin is derived from a medicinal leach.
- It acts directly on thrombin.
- Monitoring is by measuring aPTT.
- Recombinant forms of hirudin available for use include lepirudin, and desirudin. Bivalirudin is a synthetic analogue of hirudin.
- Lepirudin and bivalirudin are used in patients with HIT-type II in whom anticoagulation is required to be continued. Bivalirudin is one of the preferred drugs for patients with unstable angina undergoing percutaneous intervention.

Heparinoids

- Dermatan sulphate is a heparinoid that activates heparin cofactor II and inhibits factor X.
- Danaparoid is a mixture of anticoagulant glycosaminoglycans, predominantly low-sulphated heparan sulphate. Danaparoid has both antithrombin and anti-Xa activity, although the latter predominates (anti-Xa/antithrombin ratio ~22).
- Useful in HIT.

Factor Xa Inhibitors

- Indirect factor Xa inhibitors include fondaparinux and idraparinux.
- Enhance the rate of factor Xa inactivation by binding to antithrombin, thereby blocking thrombin generation, but have no effect on the rate of thrombin inhibition.
- Both agents have almost complete bioavailability after subcutaneous injection.
- Half-life of fondaparinux is 17 hours while that of idraparinux is 80 hours; the latter therefore can be given once a week.
- Fondaparinux approved for use in venous thromboembolic (VTE) prophylaxis in patients undergoing hip, knee or abdominal surgery, treatment of acute DVT or acute pulmonary embolism, immobilised medical patients who are at high risk for VTE, treatment of patients with non-ST-elevation acute coronary syndrome for whom urgent angiography is not indicated or treatment of patients with ST-elevation MI who are managed with thrombolytics.
- Useful in HIT-type II.
- Oral direct factor Xa inhibitors include rivaroxaban and apixaban. They directly inhibit free and prothrombinase-bound factor Xa.

Direct Thrombin Inhibitors (DTIs)

- These agents directly act on thrombin leading to inhibition of conversion of fibrinogen to fibrin. They inhibit both fibrin-bound and free thrombin.
- DTIs do not interact with heparin-platelet-factor 4 antibodies and are thereby suitable for patients with HIT type II.
- Oral thrombin inhibitors include dabigatran etexilate.
- Argatroban is another direct thrombin inhibitor that needs to be given intravenously. It is recommended in patients with HIT type II. Others which have been discussed above include hirudin, lepirudin and bivalirudin.
- Dabigatran being used for prophylaxis after hip and knee replacement, and in patients with atrial fibrillation.
- Advantages of oral direct thrombin include:
  - Rapid onset of action and hence no need for overlapping with heparin
  - Little to no food-drug interaction
  - Limited drug-drug interactions
  - No need for routine coagulation monitoring.

- Side effects include elevation in liver transaminases and possible increased rate of coronary artery disease.
- No antidote is available for overdose, bleeding or when reversal of anticoagulation is required for an emergency surgery. For bleeding, treatment is largely supportive which includes anticoagulant discontinuation, fluid resuscitation, red blood cell transfusion, diagnostic and therapeutic procedures to identify the source of bleeding, and application of local haemostatic measures. Recombinant factor VIIa (rFVIIa), prothrombin complex concentrates (PCC), and fresh frozen plasma (FFP) may be tried as potential reversal agents but they can lead to thrombotic episodes.

Q. Give a brief account of fibrinolytic system and fibrinolytic agents.

Q. Briefly describe thrombolytics.

Fibrinolysis

- Fibrinolytic system is important in normal haemostasis. Fibrinolysis is initiated by the release of either tissue plasminogen activator or pro-urokinase from the endothelial cells. These agents activate plasminogen adsorbed onto fibrin clots producing plasmin. Plasmin then degrades fibrin polymers into small fragments.

Common Indications for Fibrinolytic or Thrombolytic Agents

- Acute myocardial infarction.
- Acute peripheral artery occlusion.
- Massive pulmonary embolism with hypotension.
- Acute stroke (thrombotic or embolic).

Fibrinolytic or Thrombolytic Agents

- Most fibrinolytic or thrombolytic agents are recombinant forms with plasminogen activator activity. They have different half lives, fibrin specificity and infusion strategies. Common thrombolytics are listed below:
  - Streptokinase (STK) is obtained from β-haemolytic streptococci. On complexing with plasminogen, it converts other plasminogen molecules into plasmin. It is not fibrin-selective as it produces lysis of both fibrinogen and fibrin. Since it is derived from bacteria, it can produce allergic reactions in nearly 5% of patients. It is used in acute ST-elevation myocardial infarction and pulmonary embolism.
  - Urokinase (UK) is again not fibrin-selective. It activates plasminogen directly. It is useful in patients who received STK in the past 6 months and require a thrombolytic agent for MI or pulmonary embolism. It does not induce allergic reaction.
  - Acyl-SK-plasminogen also activates both free and fibrin-bound plasminogen.
  - Recombinant tissue plasminogen activator (rtPA) or alteplase is useful in acute thrombotic strokes (within 4.5 hours of onset) besides acute MI and pulmonary embolism. Though it is more fibrin specific compared to STK (it preferentially activates plasminogen bound to fibrin), bleeding complications with rtPA are similar with the two agents.
  - Pro-urokinase (pro-UK), like rtPA, is also fibrin specific.
  - Others are tenecteplase, reteplase and desmoteplase.

Q. Discuss blood transfusion and blood component transfusion.

Q. What are the complications of blood transfusion?

- Blood may be infused as whole blood or as component infusion. At present, almost all transfusions are in the form of transfusion of components.
- Important components of blood that are frequently used include packed red cells, platelets, fresh frozen plasma, cryoprecipitates and albumin.

Packed Red Cells

- Used when the primary aim is to increase the oxygen carrying capacity of blood.
- Can improve platelet function, particularly in uraemic patients.
- One unit of RBC can be expected to result in a rise of Hb of 1 g/dL in an adult.

General Indications for RBC Transfusion

- Symptomatic anaemia in a euvolaemic patient. In bleeding patient, replacement of intravascular volume is the first priority.
- Haemoglobin <7 g/dL in a critically ill patient with a target haemoglobin of 7–9 g/dL unless specific co-morbidities or acute illness-related factors modify clinical decision-making t.
- Haemoglobin <8 g/9g/dL in acute myocardial infarction, CHF, angina, TIA and syncope. Target is haemoglobin >9 g/dL.
- Haemoglobin <8 g/dL in patients with stable angina.
- Haemoglobin <8 g/dL in patients with thalassaemia.
- Haemoglobin <10 g/dL in a patient with uraemic bleeding.

Platelet-Rich Plasma (PRP)

- Required when bleeding occurs either due to reduced platelets or inadequate platelet function.
- One PRP bag generally increases the platelet count by 4000–8000/mm^3.
- Because platelets express the same A and B antigens as red blood cells, it is best to issue platelets that are compatible with the recipient's naturally occurring anti-A or anti-B antibodies. For example, a recipient with blood group B has anti-A antibodies and therefore can receive platelets from donors with blood group of B. Infusion of ABO non-compatible platelets is an acceptable practice, in particular when platelet concentrates are in short supply.
- Platelets can also be derived from a single donor (single donor platelets, SDP). The number of platelets that can be derived from SDR is 3×10^{11}. Apheresis platelets are indicated for patients with immune refractoriness when cross-matched or HLA matched platelets have better post-transfusion survival.

General Indications for Platelet Transfusion

- Microvascular bleeding due to thrombocytopenia or platelet dysfunction.
- Thrombocytopenia with significant risk of haemorrhage. Prophylactic platelet transfusion may be indicated if platelet count <10,000/mm^3. A higher threshold may be appropriate for patients with high fever, hyperleucocytosis, rapid fall in platelet count and coagulopathy (such as DIC).
- Surgical or invasive procedures in thrombocytopenic patients.
- In patients with autoimmune thrombocytopenias, platelet transfusion should be reserved for patients with life threatening bleeding.

Contraindication to Platelet Transfusion

- Platelet transfusion is contraindicated in thrombotic thrombocytopenic purpura (TTP) and heparin-induced thrombocytopenia (HIT).
- Relatively contraindicated in idiopathic thrombocytopenic purpura (ITP) or post-transfusion purpura (PTP) because the survival of transfused platelets is extremely brief.

Fresh Frozen Plasma

- Fresh frozen plasma (FFP) contains all the coagulation factors including von Willebrand factor.
- Plasma contains anti-A and anti-B antibodies depending upon blood group. Patients should only receive plasma which does not contain an antibody which could attack their own red cells. For example, a recipient with blood group A has anti-B antibodies and therefore can receive plasma from donors with blood group of either A or AB which has neither anti-A nor anti-B antibodies). Rh compatibility is not required.
- As FFP is not concentrated plasma, volume overload may occur if requirements are high.
- A dose of 10 mL/kg will typically provide sufficient coagulation factors to achieve haemostasis.

General Indications for Fresh Frozen Plasma Transfusion

- Single coagulation factor deficiency particularly factors V and XI deficiency.
- Consumptive coagulopathy such as DIC.
- Dilutional coagulopathy due to massive transfusion.
- Coagulopathy of liver disease.
- Microangiopathic haemolytic anaemia including TTP, haemolytic uraemic syndrome and HELLP syndrome.
- Reversal of warfarin anticoagulation (prothrombin complex concentrate is preferred in urgent situations while vitamin K is preferable if reversal in not urgent).

Compatibility of Blood Component Transfusion

Recipient's blood group	Compatible packed red cells	Compatible fresh frozen plasma	Compatible platelet-rich plasma		
			First choice	Second choice	Third choice
O	O	O, A, B, AB	O	A, B	AB
A	A, O	A, AB	A	AB	B, O
B	B, O	B, AB	B	AB	A, O
AB	AB, A, B, O	AB	AB	A, B	O

Cryoprecipitate

- Concentrate of factor VIII, von Willebrand factor, fibrinogen and factor XIII.
- Each unit contains a minimum of 80 units of factor VIII and typically 250 mg of fibrinogen.
- Does not require cross-matching before transfusion.

Factors in One Unit (10–15 mL) of Cryoprecipitate

Coagulation factor	Amount per unit	Half-life
• Fibrinogen	150–250 mg	100–150 hours
• Factor VIII	80–150 units	12 hours
• von Willebrand factor	100–150 units	24 hours
• Factor XIII	50–75 units	150–300 hours

General Indications for Cryoprecipitate Transfusion

- Factor VIII deficiency when factor VIII concentrate is not available.
- von Willebrand's disease.
- Hypofibrinogenaemia with fibrinogen <100 mg/dL (massive transfusion, congenital deficiency, and DIC).
- Factor XIII deficiency.
- Some evidence suggests that cryoprecipitate transfusion can decrease bleeding due to uraemic platelet dysfunction.

Rh Immune Globulin

- It is indicated in:
  - Known or suspected inoculation of Rh- mother with unknown or Rh+ foetal cells (threatened abortion, ectopic pregnancy, abortion, amniocentesis, abdominal trauma in 2nd or 3rd trimester, post-partum if newborn is Rh+).
  - Also indicated following transfusion of Rh+ cellular blood products (e.g. platelets) to an Rh− female of child bearing age or younger.
  - Acute ITP resistant to steroids.

Complications of Blood Transfusion

Immunological Reactions

Acute Haemolytic Transfusion Reaction

- Occurs due to transfusion of incompatible donor red cells.

Clinical features

- Early features are fever, chills, back pain, pruritus, burning sensation at the site of transfusion and centrally along the vein, and chest pain.

- In an unconscious patient, more severe features like hypotension, shock, haemoglobinuria, oliguria and excessive bleeding due to DIC develop.

Management
- Stop the transfusion immediately if a transfusion reaction is suspected.
- Change the blood transfusion set and maintain the venous access using normal saline.
- Perform physical examination with special attention to the blood pressure, urine output and evidence of bleeding.
- Withdraw blood samples from the opposite arm. Send one sample to the blood bank for evaluation and centrifuge the other sample to look for any free haemoglobin in the supernatant.
- Get a coagulation screen including partial thromboplastin time, platelet count, fibrinogen levels and fibrin-degradation products to exclude DIC.
- If hypotension develops, administer fluids and if required, vasopressors.
- Administer furosemide to maintain urine output.

Febrile Non-Haemolytic Reactions

- Generally occur due to antileucocyte antibodies in a patient who has been pregnant or has been previously transfused, reacting against leucocytes in the transfused blood.
- Can also occur due to cytokines in stored platelet concentrates.
- Generally occur towards the end of infusion or within hours of completing the transfusion.
- Management is symptomatic with antipyretics.
- Incidence can be reduced by leucoreduction in which WBCs are reduced in number through centrifugation or filtration.

Urticaria

- Due to the presence of antibodies in the recipient's blood to infused plasma proteins or infusion of allergens that react with IgE antibodies in the patient.

Anaphylaxis

- Occurs in patients who have antibodies against IgA and are often deficient in IgA. The antibodies react with IgA present in the donor blood.

Transfusion-Related Acute Lung Injury (TRALI)

- The donor plasma has antibodies to patient's leucocytes. Such antibodies are found most frequently in females after pregnancy and are not present in plasma of males unless they have been transfused.
- Patient develops an acute respiratory reaction with fever, cough, shortness of breath and typical appearance on chest X-ray. The reaction occurs during or soon after transfusion and may be life threatening.

Delayed Haemolytic Transfusion Reaction

- It occurs 3–21 days after transfusion with the incompatible blood. Patient has IgG antibodies to the red cell antigens such as Rh, Kidd, Kell, Duffy because of previous pregnancies or transfusions. The antibodies are undetectable during cross-match but further transfusion causes a secondary immune response resulting in delayed haemolysis.
- Direct Coombs' test will be positive if carried out while the patient is actively haemolysing. Later, only indirect Coombs' test may be positive.

Transfusion-Associated Graft-Versus-Host Disease (TA-GVHD)

- It occurs due to immune reaction of donor T cells against the recipient who is often immunodeficient, e.g. bone marrow allograft recipient, Hodgkin's lymphoma.
- Clinically, patient develops fever, skin rash, liver and renal failure, and pancytopenia. It develops 4–30 days after transfusion and may be fatal.
- Prevention is by using gamma-irradiation of cellular blood components.

Post-Transfusion Purpura

- It is an immune-mediated thrombocytopenia that usually occurs in parous females.
- Antibodies against human platelet antigens (HPAs) are detectable in the patient's serum.
- It occurs 5–12 days after transfusion.

- Thrombocytopenia is usually severe and may cause bleeding.
- Platelet transfusions are usually ineffective and the treatment of choice is high-dose intravenous immunoglobulins (0.4 g/kg/day for 5 days).

Non-Immune Reactions

- Transfusion associated circulatory overload (TACO), especially in patients with renal and cardiac failure.
- Adverse effects of massive transfusion—e.g. hyperkalaemia, ammonia and citrate toxicity, and thrombocytopenia.
- Infections—e.g. viral hepatitis, HIV, syphilis, malaria and CMV infections.
- Air and fat embolism.
- Thrombophlebitis.
- Haemosiderosis as 1 unit of RBCs contains 200–250 mg of iron.

Q. Discuss the differential diagnosis of generalised lymphadenopathy in an adult.

Assessment of the Extent of Lymph Nodal Enlargement

- Clinical evaluation of lymph nodes should include the sites of enlargement, size, consistency, character, fixity and presence or absence of tenderness. Associated other systemic abnormalities should be noted.
- Chest X-ray and CT scan of the thorax can detect mediastinal, hilar and paratracheal lymphadenopathy.
- Ultrasound scanning and CT scan of abdomen can detect intra-abdominal lymph nodes.

Cause	Diagnostic feature
- Lymphomas (Hodgkin's, non-Hodgkin's)	Histology of lymph node
- Leukaemias (ALL, CLL, CML in blast crisis)	Peripheral smear and bone marrow
- Disseminated tuberculosis	Caseating granulomas in lymph node
- Human immunodeficiency virus infection	ELISA and western blot
- Secondary syphilis	VDRL and TPHA
- Infectious mononucleosis	Monospot test and Paul–Bunnell test
- Brucellosis	Brucella agglutination test
- Systemic lupus erythematosus	ANA
- Rheumatoid arthritis	Rheumatoid factor
- Metastatic disease (head and neck cancers, lung and breast cancers, GIT malignancies)	Fine needle aspiration and biopsy
- Local infections (cellulitis, pharyngitis)	Local examination
- Plague	Inguinal lymph nodes; FNAC shows typical "safety pin" bacteria

Differential Diagnosis

Lymphomas (Hodgkin's and non-Hodgkin's)

Clinical Features

- Systemic symptoms like fever, weight loss and night sweats.
- Pel–Epstein type of fever.
- Pruritus.
- Alcohol-induced pain in the lymph nodes.
- Clinical effects of pressure by lymph node masses on neighbouring structures.
- Painless, discrete, rubbery lymph nodes.

Lab Features

- Lymph node biopsy confirms the diagnosis.

Acute Lymphoblastic Leukaemia

Clinical Features

- Common in children.
- Bleeding manifestations.

- Intermittent infections and fever.
- Severe anaemia.
- Bone pain and sternal tenderness.
- Hepatosplenomegaly.
- Frequent testicular, central nervous system and eye involvement.

Lab Features

- Blood examination shows severe anaemia of normochromic type, raised total leucocyte count, presence of lymphoblasts and other primitive cells, and thrombocytopenia.
- More than 50% of the cells are periodic acid—Schiff (PAS)-positive on cytochemical staining.
- Bone marrow is hypercellular with the replacement of normal elements by leukaemic blast cells.

Chronic Lymphocytic Leukaemia

Clinical Features

- More in males over 50 years, with peak incidence around 65 years.
- Firm, rubbery, discrete, painless lymph nodes.
- Hepatosplenomegaly.

Lab Features

- Anaemia.
- Total leucocyte count is raised.
- More than 95% of the leucocytes in the peripheral blood are lymphocytes of small variety.
- Bone marrow is hypercellular with infiltration of small and medium-sized lymphocytes.
- Lymph node biopsy shows well-differentiated, small, non-cleaved lymphocytes.

Chronic Myeloid Leukaemia in Blast Crisis

Clinical Features

- Common in elderly people, average age around 55 years.
- The usual patient is one who had been diagnosed and treated for chronic myeloid leukaemia. Such a patient suddenly develops features of acute leukaemia—e.g. fever, bleeding manifestations, anaemia, bony tenderness, abrupt increase in splenic size and refractoriness to treatment.
- Massive splenomegaly.

Lab Features

- Blood and bone marrow findings are indistinguishable from acute leukaemia, with plenty of blast cells.
- Philadelphia chromosome is positive in more than 95% of the cases.

Disseminated Tuberculosis

Clinical Features

- Fever, weight loss, night sweats and loss of appetite.
- Usually the patient is toxic.
- Hepatosplenomegaly may be present.

Lab Features

- Chest X-ray might show miliary mottling.
- Lymph node biopsy shows caseating granulomas.
- Liver biopsy may show granulomas.

Human Immunodeficiency Virus (HIV) Infection

Clinical Features

- Common after heterosexual contact with HIV-positive person. Also occurs in intravenous drug abusers, haemophiliacs (due to transfusion of blood from HIV$^+$ persons) and homosexuals.
- Generalised lymphadenopathy can occur in three situations:
  - Immediately after acquiring infection (within 2–3 weeks).
  - Persistent generalised lymphadenopathy (PGL) or AIDS-related complex (ARC).
  - As a part of full-blown AIDS.

Lab Features

- ELISA test for HIV antibody (screening test).
- Western blot test that identifies antibodies to specific viral proteins (confirmatory test).

Secondary Syphilis

Clinical Features

- Past history of exposure and primary syphilis (genital ulcers and inguinal lymphadenopathy).
- Generalised skin rashes.
- Condylomata lata.
- Mucous patches and snail-track ulcers.
- Hepatosplenomegaly.
- Discrete, "shotty" lymph nodes.

Lab Features

- Dark field microscopy can demonstrate *Treponema pallidum* in papules and mucous patches.
- Positive VDRL test.
- Positive *Treponema pallidum* haemagglutination test (TPHA).

Infectious Mononucleosis

Clinical Features

- Fever of short duration.
- Maculopapular rash.
- Petechial haemorrhages on palate.
- Hepatosplenomegaly.

Lab Features

- Atypical lymphocytes in the peripheral blood.
- Positive Monospot test.
- Positive Paul–Bunnell test.

Brucellosis

Clinical Features

- Common in veterinary surgeons and slaughterhouse workers handling cattle.
- Fever, polyarthritis, splenomegaly.

Lab Features

- Positive blood culture.
- Positive Brucella agglutination test.
- Positive complement fixation and antihuman globulin tests.
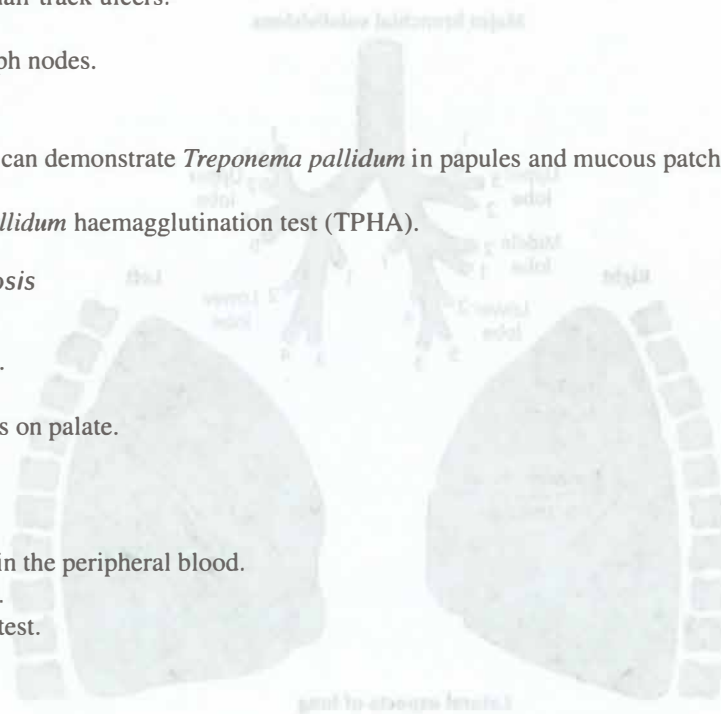
Chapter 2
Diseases of the Respiratory System

Q. Define a bronchopulmonary segment. Name the bronchopulmonary segments.

- Bronchopulmonary segment is a wedge of lung tissue supplied by one segmental bronchus along with the corresponding branches of pulmonary artery and pulmonary vein. Each segment is an independent unit and these units are separated from each other by fibrous septa.

Major bronchial subdivisions

Lateral aspects of lung
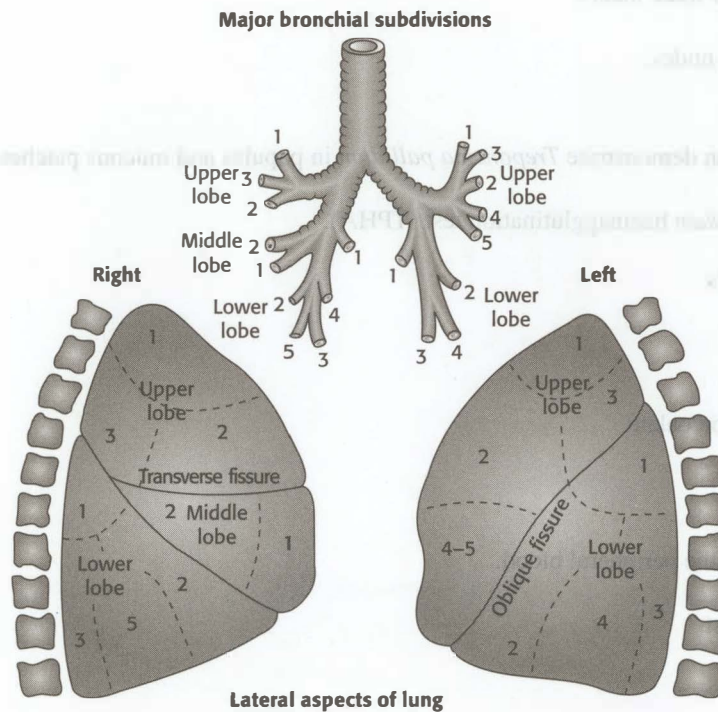
Bronchopulmonary segments:
Right—*Upper lobe*. 1. Apical, 2. Anterior, 3. Posterior; *Middle lobe*. 1. Medial, 2. Lateral; *Lower lobe*. 1. Apical, 2. Anterior basal, 3. Posterior basal, 4. Medial basal, 5. Lateral basal.
Left—*Upper lobe*. 1. Apical, 2. Anterior, 3. Posterior, 4. Superior (lingular), 5. Inferior (lingular); *Lower lobe*. 1. Apical, 2. Anterior basal, 3. Posterior basal, 4. Lateral basal.

Segmental Bronchi and Bronchopulmonary Segments

Right lung	Left lung

• Upper lobe
  • Apical bronchus and segment
  • Anterior bronchus and segment
  • Posterior bronchus and segment
• Middle lobe
  • Medial bronchus and segment
  • Lateral bronchus and segment
• Lower lobe
  • Apical bronchus and segment
  • Anterior basal bronchus and segment
  • Posterior basal bronchus and segment
  • Medial basal bronchus and segment
  • Lateral basal bronchus and segment
	• Upper lobe
	  • Apical bronchus and segment
	  • Anterior bronchus and segment
	  • Posterior bronchus and segment
	  • Superior (lingular) bronchus and segment
	  • Inferior (lingular) bronchus and segment
	• Lower lobe
	  • Apical bronchus and segment
	  • Anterior basal bronchus and segment
	  • Posterior basal bronchus and segment
	  • Lateral basal bronchus and segment

Q.   Give the normal arterial blood gas (ABG) levels.

• Arterial oxygen tension	PaO_2	95 ± 5 mmHg
• Arterial carbon dioxide (CO_2)	$PaCO_2$	40 ± 2 mmHg
• Arterial oxygen saturation	SaO_2	$97 \pm 2\%$
• Arterial blood pH	pH	7.40 ± 0.02
• Arterial bicarbonate	HCO_3	24 ± 2 mmol/L
• Base excess	BE	0 ± 2 mmol/L

Q.   Discuss the causes, mechanisms, clinical features, investigations and management of hypercapnic encephalopathy [carbon dioxide (CO_2) narcosis].

Definition

• Hypercapnia is defined as a $PaCO_2$ in excess of 45 mmHg (6 kPa) at rest.
• CO_2 narcosis may occur when $PaCO_2$ exceeds 90 mmHg (12 kPa).

Causes

Central	Chest wall
• Brainstem lesions • Central sleep apnoea	• Kyphoscoliosis • Ankylosing spondylitis • Trauma
Neuromuscular	**Pulmonary**
• Peripheral neuropathy • Myasthenia gravis • Myopathies	• Chronic bronchitis • Emphysema

Mechanisms

- Decreased ventilatory drive ("won't breathe").
- Malfunction of the respiratory pump or increased airway resistance ("can't breathe").
- Inefficiency of gas exchange (increased dead space or V/Q mismatch).
- Increased carbon dioxide (CO_2) production.

Clinical Features

- Intense headache that is generalised or bilateral frontal or occipital. It is especially severe on waking up.
- Intermittent drowsiness, indifference or inattention, reduction of psychomotor activity and forgetfulness occur in mild cases.
- Mental dullness, drowsiness, confusion, stupor and coma occur in severe cases.

Signs

• Fast-frequency action tremor	• Bounding peripheral pulses	• Muscle twitching (fasciculations)
• Flushed warm extremities	• Flapping tremor (asterixis)	• Papilloedema

Investigations

- ABG studies confirm hypercapnia.
- Relevant investigations in relation to the underlying aetiology.

Treatment

- Mechanical ventilation with intermittent positive pressure respirator. In a selected group of patients with mild symptoms, non-invasive ventilation (NIV) may be tried.
- Correction of acidosis and electrolyte imbalance.
- Treatment of underlying disorder

Note

- Patients with chronic hypercapnia [e.g. chronic obstructive pulmonary disease (COPD)] are particularly vulnerable to the effects of oxygen and drugs like morphine and sedatives. Oxygen abolishes the hypoxic drive to ventilation and drugs depress the respiratory centre in the brain, both of which may cause a disastrous worsening of hypercapnia.
- Hence, in patients with chronic hypercapnia, oxygen should be administered in a controlled manner (about 2 L/minute) and drugs like morphine and sedatives should better be avoided.

Q. Discuss the causes, clinical features and management of hypoxaemia.

Definition

- Hypoxaemia is defined as a PaO_2 of less than 80 mmHg (10.6 kPa) in a young healthy adult. However, the normal PaO_2 falls gradually as the age advances.
- Hypoxaemia indicates abnormally low PaO_2 while the term hypoxia indicates inadequate tissue oxygenation. These terms are not interchangeable. A person can be hypoxaemic without hypoxia and similarly a person can be hypoxic without hypoxaemia. For example, if a person is hypoxaemic but has polycythemia, he may not have tissue hypoxia. Similarly, a severely anemic patient may have tissue hypoxia without hypoxaemia.

Causes

Ventilation-perfusion mismatching	Hypoventilation
• Chronic bronchitis	• Brainstem lesions
• Emphysema	• Central sleep apnoea
• Acute asthma	• Peripheral neuropathy
• Interstitial lung diseases	• Myasthenia gravis
• Pulmonary embolism	• Myopathies
	• Malfunctioning of mechanical ventilators
Right-to-left shunts	**Reduced inspired oxygen concentration**
• Congenital cyanotic heart diseases	• High altitudes
• Pulmonary atelectasis	• Malfunctioning of mechanical ventilators
• Pneumonia	

- Hypoxaemia is uncommon due to reduced diffusion.

Clinical Features

- Acute hypoxaemia is characterised by impaired judgement, motor incoordination and a clinical picture closely resembling acute alcoholism.
- Long-standing hypoxaemia is characterised by fatigue, drowsiness, inattentiveness, apathy, delayed reaction time and reduced work capacity.
- Finally, centres in the brainstem are affected and death results from respiratory failure.

Investigations

- ABG studies confirm hypoxaemia.
- It is useful to calculate the alveolar-arterial oxygen (PAO_2-PaO_2) gradient for differentiating various causes of hypoxaemia (see pulmonary function tests and respiratory failure). It is normal in patients with pure hypoventilation and reduced inspired oxygen concentration.

Treatment

- Treatment is that of the underlying disease or mechanism.

Q. Define clubbing. Enumerate the causes and give the mechanism of clubbing.

Definition

- Clubbing is defined as a selective bulbous enlargement of the distal segment of a digit due to an increase in soft tissue.
- Pseudoclubbing is increased in longitudinal curvature of the nail with loss of nail plate material and is seen in scleroderma, thyroid carcinoma and sarcoidosis. X-ray of fingers show resorption of terminal tufts (acro-osteolysis) instead of an overgrowth of phalangeal tufts seen in clubbing. Finger involvement is asymmetrical as compared to clubbing.

Mechanisms

- Humoral theory states that an unidentified humoral substance causes dilatation of vessels of the finger tip.
- Persistent hypoxia causes opening up of the deep arteriovenous fistulae of fingers.
- Reduced ferritin in the systemic circulation causes dilatation of the arteriovenous anastomoses and hypertrophy of the terminal phalanx.
- Vagal theory states that persistent vagal stimulation causes vasodilatation and clubbing.
- Recent studies have suggested a possible role of platelets in the development of clubbing particularly hypertrophic osteoarthropathy. It is postulated that circulating megakaryocytes and large platelet particles, normally destroyed by the lungs, reach distal extremities and interact with endothelial cells resulting in the liberation of platelet-derived growth factor (PDGF) and other factors. These factors cause proliferation of the connective tissue.
- Unilateral clubbing may occur in neurologic (hemiplegia) and vascular disorders (dialysis fistula and AV malformations).

Grading of Clubbing

• Grade I	Increased fluctuation of the nail bed
• Grade II	Obliteration of the angle between nail and nail bed (Lovibond angle; normal ≤160°)
• Grade III	Increased curvature of the nail resulting in a parrot beak or drumstick appearance
• Grade IV	Hypertrophic osteoarthropathy, characterised by digital clubbing, arthritis, and periostitis of the long bones resulting in painful, tender, swelling of wrists (most common), ankles, elbows and knees

Common Causes of Clubbing

Respiratory causes
- Bronchogenic carcinoma
- Bronchiectasis
- Lung abscess
- Empyema
- Mesothelioma
- Long-standing tuberculosis
- Pulmonary AV fistula
- Interstitial lung diseases

Cardiac causes
- Infective endocarditis
- Congenital cyanotic heart diseases

Alimentary causes
- Ulcerative colitis
- Crohn's disease
- Cirrhosis of liver
- Hepatoma

Miscellaneous causes
- Hereditary, idiopathic
- Thyrotoxicosis
- Acromegaly
- Unilateral clubbing in Pancoast's tumour, subclavian artery aneurysm and hemiplegia
- Unidigital clubbing occurs in repeated trauma

HIV infection

Examination for Clubbing

- Clubbing can be assessed by asking the patient to place the dorsum of fourth finger of the opposite hands in opposition. Normally, an open diamond-shaped window is visible between the opposing nails due to the presence of Lovibond angle. Obliteration of this area indicates the presence of clubbing. This is known as Schamroth's sign.
- An objective measurement of finger clubbing can be made by determining the diameter at the base of nail and at the distal interphalangeal joints of all 10 fingers and calculating the digit ratio for each finger. Clubbing is present when the sum of the individual digit ratio is greater than 10.
- Another method is to calculate the phalangeal depth ratio. Normally, the distal phalangeal depth is smaller than the depth of the interphalangeal joint. To perform this test, calipers should be used. The calipers should touch but not compress the skin. For clubbing to be present, the distal phalangeal depth: interphalangeal joint depth ratio should exceed 1.0. The index finger is the suggested digit used for measurement.

Q. Describe abnormalities in nails due to systemic diseases.

Abnormalities in Nails Due to Systemic Diseases

Abnormality	Description	Systemic causes
• Clubbing	Discussed above	Discussed above
• Koilonychia	Spoon-shaped nails (transverse and longitudinal concavity)	Iron deficiency anaemia, haemochromatosis, Raynaud's disease, SLE, chronic exposure of hands to petroleum-based solvents, hypothyroidism or hyperthyroidism
• Pitting	Punctate depressions in nails	Psoriasis, Reiter's syndrome, sarcoidosis, pemphigus, lichen planus, alopecia areata, rheumatoid arthritis
• Onycholysis	Distal nail plate separated from nail bed, resulting in white discoloration of the affected part of the nail	Psoriasis, local infection, hyperthyroidism (Plummer's nail—onycholysis of fourth and fifth digits), sarcoidosis, amyloidosis, connective tissue disorders, pellagra
• Onychomadesis	Proximal separation of nail plate from nail bed; often results in shedding of the nail	Trauma, drug sensitivity, poor nutrition, pemphigus vulgaris, Kawasaki disease, hand-foot-mouth disease
• Beau's lines	Transverse linear depressions over nails (occurring at same spot in most nails); move distally with the growth of nail	Severe systemic illness that disrupts nail growth, Raynaud's disease, pemphigus
• Yellow nails	Nail has a "heaped-up" or thickened appearance, yellow in colour, with obliteration of lunula	Lymphoedema, pleural effusion, immunodeficiency, bronchiectasis, nephrotic syndrome, thyroiditis, tuberculosis
• Terry's (white) nails	Most of the nail plate turns white with obliteration of lunula; all the nails uniformly affected	Liver failure, cirrhosis, diabetes mellitus, CHF, hyperthyroidism, malnutrition
• Half-and-half nails (Lindsay's nails)	Proximal portion of nail bed is white because of nail-bed oedema (half-brown, half-white appearance)	Renal failure, HIV infection, Crohn's disease
• Mees' lines	Transverse white bands frequently affecting multiple nails; move distally with growth of nail	Arsenic and thallium poisoning, Hodgkin's disease, CHF, leprosy, malaria
• Muehrcke's lines	Pairs of transverse white lines; disappear on applying pressure; do not move with growth of nail	Hypoalbuminaemia due to any cause
• Splinter haemorrhage	Longitudinal, thin, reddish lines occurring beneath the nail plate	Subacute bacterial endocarditis, SLE, rheumatoid arthritis, oral contraceptive use, pregnancy, psoriasis, trauma, trichinosis, scurvy
• Telangiectasia	Irregular, twisted and dilated vessels at the distal portion of cuticle covering the nail bed	Rheumatoid arthritis, SLE, dermatomyositis, scleroderma

Q. Enumerate the pulmonary function tests and give their clinical significance.

Pulmonary Function Tests

- Ventilatory capacity (FEV$_1$, FVC, PEF)
- Reversibility of airflow limitation (by administering inhaled bronchodilator)
- Flow-volume curves

- Airway resistance
- Gas transfer (diffusion)
- Lung volumes (TLC, RV)

- Blood gases
- Pulse oximetry
- Exercise tests

Abbreviations used in Pulmonary Function Tests

FEV$_1$	Forced expiratory volume in one second	FRC	Functional residual capacity
FVC	Forced vital capacity	RV	Residual volume
VC	Vital capacity	DLCO	Diffusing capacity of the lungs for
PEF	Peak expiratory flow		carbon monoxide
TLC	Total lung capacity		

Ventilatory Capacity

- Forced expiratory volume in one second (FEV$_1$), forced vital capacity (FVC) and vital capacity (VC) are recorded using a spirometer. The patient inhales fully and then forcibly exhales as fast as possible into the mouth piece of the spirometer until no more air can be expelled. A chart records the volume exhaled against time. From this, both FEV$_1$ and FVC can be measured.
  - FVC is the volume of air expired with a maximal effort after deep inspiration.
  - FEV$_1$ is the volume of air expired in the first second after deep inspiration.
  - VC is recorded separately by asking the patient to make a full but unhurried ("relaxed") exhalation into the spirometer.
- Two typical patterns of abnormalities can be found:
  1. Obstructive ventilatory defect, where there is narrowing of airways during expiration (e.g. bronchial asthma and chronic bronchitis). Here FEV$_1$ is markedly decreased, VC is decreased or normal and FEV$_1$/VC is decreased.
  2. Restrictive ventilatory defect, where FEV$_1$ and VC are decreased and FEV$_1$/VC is normal or increased.
- Peak expiratory flow rate (PEF) can be measured during forced expiration by a gauge or metre, which is simpler and cheaper than a spirometer. It measures the maximum flow generated during expiration performed with maximal force and started after a full inspiration. Reduced values indicate airflow obstruction. It is of no use in restrictive ventilatory defect.

Reversibility of Airflow Limitation

- If an obstructive ventilatory defect is found, the responses to bronchodilators (salbutamol) can be measured.
- Reversibility of airflow obstruction is seen in bronchial asthma and to some extent, in chronic obstructive pulmonary disease.

Lung Volumes

- Values are obtained either by diluting helium into gas in the lungs or in the whole body plethysmograph.
- Lung volumes include total lung capacity (TLC) and residual volume (RV). TLC is the amount of air in the lungs at the end of full inspiration. RV is the volume of air in the lungs at the end of full expiration.
- These measurements are not dependent on the effort (unlike spirometry methods).
- They are helpful in differentiating obstructive from restrictive lung diseases.
- Both TLC and RV are increased in patients with obstructive lung disease while they are reduced in restrictive lung diseases due to parenchymal diseases. In extraparenchymal diseases with restriction during both inspiration and expiration (ankylosing spondylitis and kyphoscoliosis), RV is increased while TLC is reduced.
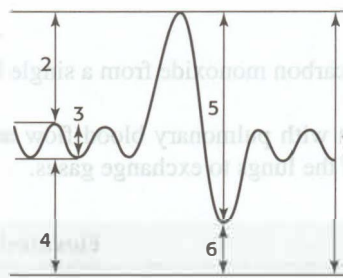
1 = Total lung capacity
2 = Inspiratory reserve volume
3 = Tidal volume
4 = Functional residual capacity
5 = Vital capacity
6 = Residual volume

Flow-Volume Curves

- These curves measure flow rates against volume. This helps in analysing the site of obstruction within the lung.
- At the start of expiration the site of maximum resistance is the large airways, which is reflected in the first 25% of the curve. As the lung volume reduces further, the smaller airways are responsible for most of the resistance. Therefore, calculation of flow rates at 50% and 75% of the VC may be disproportionately reduced in patients with early chronic obstructive airway disease.
- FEF25-75 is the maximal flow rate in the mid portion of expiration, i.e. 25-75%. It is a sensitive index of small airway function.
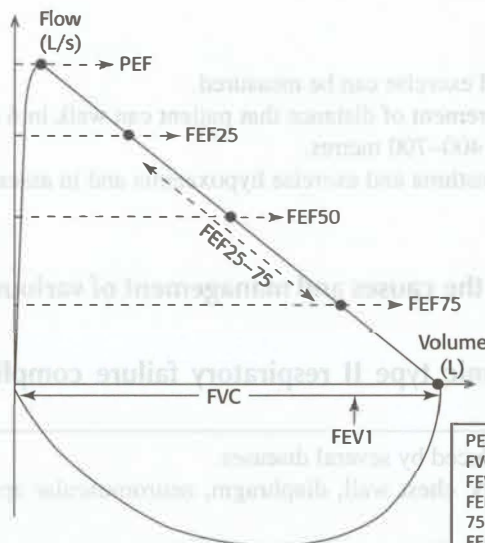
PEF = Peak expiratory flow
FVC = Forced vital capacity
FEV1 = Forced expiratory volume in one second
FEF25, 50, 75 = Forced expiratory flow at 25%, 50% and 75% exhalation of forced vital capacity
FEF25-75 = forced expiratory flow between 25-75% of forced vital capacity

Arterial Blood Gas Analysis

- Arterial blood gas (ABG) studies are done with automatic analysers. They measure PO_2, PCO_2 and H^+ concentration in the arterial blood. Oxygen saturation and bicarbonate concentration can be derived from the above values.
- Studies are extremely useful in the management of respiratory failure, status asthmaticus and acute respiratory distress syndrome (ARDS).
- Alveolar-arterial oxygen (PAO_2-$0PaO_2$) or P (A-a)O_2 gradient:
  - Useful to interpret PaO_2 when $PaCO_2$ is abnormal, which can occur due to hypoventilation or other reasons.
  - $PAO_2 = FiO_2 \times (P_B - P_{H_2O}) - PaCO_2/R$, where FiO_2 is the oxygen fraction in inspired air (0.21 if breathing air), P_B is barometric pressure (760 mmHg at sea level), P_{H_2O} is water vapour pressure (47 mmHg when air is saturated with water) and R is respiratory quotient (the ratio of CO_2 production to oxygen consumption and is assumed to be 0.8). At sea level, $PAO_2 = 150 - (1.25 \times PaCO_2)$.
  - Normal alveolar arterial oxygen gradient is (Age + 10)/4. For any age, this gradient is not more than 20 mmHg.
  - A higher gradient in young person reflects impairment of alveolar oxygenation.

Diffusion Capacity

- Diffusing capacity is estimated by measuring uptake of carbon monoxide from a single breath of a air containing 0.3% carbon monoxide and 10% helium.
- It gives an estimate of matching of alveolar ventilation with pulmonary blood flow and not the diffusion of carbon monoxide. In effect, it gives an estimate of the ability of the lungs to exchange gases.

Reduced diffusion capacity	Elevated diffusion capacity
• Interstitial lung diseases • Sarcoidosis • Emphysema • Smokers • Anaemia • Pulmonary vascular diseases—chronic recurrent pulmonary emboli, idiopathic pulmonary arterial hypertension, pulmonary vascular involvement with connective tissue diseases (e.g. systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis)	• Severe obesity • Asthma • Polycythemia • Pulmonary haemorrhage • Left-to-right intracardiac shunting

Exercise Tests

- Cardiac and respiratory response to bicycle or treadmill exercise can be measured.
- Simple method ("everyday" exercise test) is the measurement of distance that patient can walk in 6 minutes. During a 6 minute walk test, healthy subjects can typically walk 400–700 metres.
- Exercise tests are useful in detecting exercise-induced asthma and exercise hypoxaemia and in assessing the disability due to respiratory diseases.

Q. Define respiratory failure. Describe in detail the causes and management of various types of respiratory failures.

Q. Discuss the role of oxygen therapy in chronic type II respiratory failure complicating chronic obstructive pulmonary disease.

- Respiratory failure is not a disease but a condition produced by several diseases.
- Respiratory failure may result from disorders of lungs, chest wall, diaphragm, neuromuscular apparatus or central nervous system.
- It may develop within minutes to a few days when it is called acute respiratory failure or may develop over weeks to months when it is called chronic respiratory failure.
- Consider respiratory failure in a patient with following features and measure ABG in all such patients.

• Breathlessness at rest • Central cyanosis	• Raised respiratory rate • Drowsiness, confusion or unconsciousness

Definition and Classification

- Respiratory failure is present when PaO_2 is <60 mmHg (8.0 kPa) and/or $PaCO_2$ is >50 mmHg (6.5 kPa).
  - Type I respiratory failure is characterised by low PaO_2 and low or normal $PaCO_2$.
    - Acute hypoxaemia without hypercapnia (acute type I respiratory failure)
    - Chronic hypoxaemia without hypercapnia (chronic type I respiratory failure)

- Type II respiratory failure is characterised by low PaO_2 and raised $PaCO_2$.
  - Acute hypoxaemia with hypercapnia (acute type II respiratory failure)
  - Chronic hypoxaemia with hypercapnia (chronic type II respiratory failure)
  (Note that hypoxaemia is invariable in respiratory failure, but hypercapnia may or may not be present)
- Uncommon types of respiratory failure are type III and type IV.
- Type III respiratory failure occurs in perioperative period and occurs due to several reasons like postoperative pain leading to shallow breathing, atelectasis causing low functional residual capacity and use of narcotics causing respiratory depression. Treatment is by maintaining upright posture, incentive spirometry, chest physiotherapy, post-operative analgesia and lowering of intra-abdominal pressure.
- Type IV respiratory failure occurs in patients with shock like those with cardiogenic shock, septic shock or hypovolaemic shock. Due to shock, the oxygen delivery to respiratory muscles is reduced. In addition, the metabolic demand of body is increased.

Mechanisms Producing Respiratory Failure

● Decreased inspired oxygen concentration	High altitude—acute mountain sickness, chronic mountain sickness
● Hypoventilation	Diminished ventilatory drive—drug overdose, primary alveolar hypoventilation, stroke
	Impaired neuromuscular transmission—Guillain–Barre syndrome, phrenic nerve injury, spinal cord lesion, amyotrophic lateral sclerosis, myasthenia gravis
	Muscle weakness—myasthenia gravis, muscular dystrophies, electrolyte disturbances, respiratory muscle fatigue
	Chest wall disorders—kyphoscoliosis, ankylosing spondylitis, flail chest, severe obesity
	Pleural disorders—pneumothorax, pleural effusion
	Parenchymal lung disease
	Airway obstruction—COPD, acute severe asthma, foreign body, vocal cord palsy
● Ventilation-perfusion (V/Q) mismatch	Interstitial lung disease
	Obstructive airway disease—chronic bronchitis, emphysema, bronchiectasis, asthma
	Alveolar diseases—pneumonia, acute respiratory distress syndrome (ARDS)
	Pulmonary vascular diseases—pulmonary embolism, pulmonary hypertension
	Decreased cardiac output
● Shunt	Intracardiac right-to-left shunts—tetralogy of Fallot, Eisenmenger syndrome
	Intrapulmonary shunts—pulmonary arteriovenous shunts, alveolar collapse, pneumonia, pulmonary oedema, pulmonary haemorrhage
● Diffusion abnormality	Interstitial lung disease, ARDS, interstitial pneumonias

- Alveolar ventilation is tidal volume minus dead space multiplied by respiratory rate. Hypoventilation can therefore, occur due to low tidal volume, increased dead space or reduced respiratory rate. In hypoventilation, $PaCO_2$ increases while PaO_2 decreases. Alveolar-arterial oxygen gradient is normal.

- V/Q mismatch is the most common cause of hypoxaemia. In V/Q mismatch, administration of 100% O_2 will markedly improve hypoxaemia. Alveolar-arterial oxygen gradient is elevated.
- If a shunt is present, deoxygenated blood bypasses ventilated alveoli and mixes with oxygenated blood to cause hypoxaemia. In shunts, hypoxaemia will persits even if patient is given 100% oxygen. Hypercapnia is not common and will occur when shunt fraction is more than 60%. Alveolar-arterial oxygen gradient is elevated.
- Impairment of diffusion is an uncommon cause of hypoxaemia. This is because blood has sufficient time to get oxygenated while passing through pulmonary capillaries. Impairement of diffusion is seen in interstitial lung diseases, ARDS and interstitial pneumonias but the major causes of hypoxaemia in these conditions are V/Q mismatch and shunts.
- In acute respiratory failure, pH of blood may drop to below 7.2 while in chronic, pH is normal or slightly reduced and bicarbonate is elevated due to renal compensation. Due to associated hypoxaemia, patient with chronic respiratory failure may develop polycythaemia, pulmonary hypertension and cor pulmonale.

Acute Type I Respiratory Failure

Common Causes

- These disorders typically have an abrupt onset, often in patients with previously normal lungs.

- Pneumonia	- Acute asthma
- Pulmonary oedema	- Pulmonary embolism
- Acute respiratory distress syndrome (ARDS)	- Pneumothorax

Management

- Treat the underlying condition.
- High concentrations (40–60%) of oxygen through oronasal mask.
- Most patients recover with treatment of underlying disease and oxygen therapy, but a few very ill patients may require artificial ventilation.

Chronic Type I Respiratory Failure

Causes

- Diseases associated with widespread pulmonary fibrosis	- Chronic chest wall or neuromuscular diseases
- Chronic pulmonary oedema	- Chronic pulmonary thromboembolism

Management

- Treatment of the underlying causes wherever possible.
- Oxygen therapy, which may be intermittent or at times long term.
- Artificial ventilation may be tried, but in general the prognosis is poor.
- Venesection to reduce haematocrit in patients with severe secondary polycythaemia.
- Diuretics to reduce peripheral oedema.

Acute Type II Respiratory Failure

Causes

- Respiratory depressant drugs like diazepam, opiates and alcohol
- Brainstem damage from stroke, encephalitis and trauma
- Disorders of spinal cord, nerves and neuromuscular transmission like spinal trauma, transverse myelitis, acute GB syndrome, poliomyelitis, myasthenia gravis and botulism
- Disorders of muscle affecting respiratory muscles like acute polymyositis
- Severe airflow obstruction like severe acute asthma, laryngeal and tracheal obstruction, acute exacerbation of chronic obstructive pulmonary disease (COPD)
- Chest injuries resulting in tension pneumothorax, massive haemothorax and flail chest

Management

- Treatment of the underlying condition.
- Oxygen therapy to be started with 24% oxygen and adjusted further based on serial measurements of ABG levels.
- Removal of secretions by coughing or emergency bronchoscopic aspiration.
- Bronchodilators in severe airflow obstruction.
- Assisted ventilation (invasive or non-invasive) must be considered in selected cases.

Chronic Type II Respiratory Failure

Causes

- COPD (most common)
- Chest wall abnormalities like gross kyphoscoliosis, muscle weakness and gross obesity
- Amyotrophic lateral sclerosis, muscular dystrophy
- Central hypoventilation

Management

- Treatment of the underlying causes.
- Oxygen therapy carries the risk of causing depression of ventilation if respiratory drive has been dependent on hypoxaemia. Correction of hypoxaemia will then cause a further rise in $PaCO_2$ resulting in confusion, drowsiness or loss of consciousness. Think carefully before prescribing oxygen to such patients. However, oxygen is indicated in selected cases. Note the following points on oxygen therapy:
  - Measure ABG levels before oxygen therapy.
  - Do not give more than 24% oxygen initially.
  - Give oxygen continuously and not intermittently. It is preferable to give oxygen at a rate of 1–2 L/minute.
  - Oxygen therapy should be monitored by serial ABG measurements and/or pulse oximetry. In selected cases, oxygen concentration can be increased to 28–32%.
  - Respiratory stimulants like doxapram hydrochloride can increase or maintain ventilation for a short time, at most 24 hours. However, its role is controversial.
  - Mechanical ventilation is reserved for selected cases who fail to respond to all other measures.
  - Supportive treatment includes antibiotics for respiratory infection, nebulised bronchodilators, clearing secretions by coughing, suction, chest physiotherapy, etc. and diuretics for oedema.

Approach to Respiratory Failure

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                              ┌──────────────┐
                              │  Hypoxaemia  │
                              └──────┬───────┘
                                     │
                              ┌──────┴───────┐
                              │   PaCO₂      │
                              └──────┬───────┘
              ┌──────────────────────┴──────────────────────┐
        ┌─────┴──────┐                              ┌────────┴───────┐
        │ Increased  │                              │  Normal or low │
        └─────┬──────┘                              └────────┬───────┘
   ┌──────────┴────────────────────┐        ┌────────────────┴────────────────────┐
   │ Measure alveolar-arterial     │        │ Measure alveolar-arterial           │
   │ oxygen gradient               │        │ oxygen gradient                     │
   └──────────┬────────────────────┘        └────────────────┬────────────────────┘
      ┌───────┴────────┐                          ┌───────────┴───────────┐
  ┌───┴───┐     ┌──────┴───┐               ┌──────┴───┐          ┌─────────┴─┐
  │Normal │     │Increased │               │Increased │          │  Normal   │
  └───┬───┘     └──────┬───┘               └──────┬───┘          └─────────┬─┘
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| Hypoventilation alone (e.g. sleep apnoea, central hypoventilation, drug overdose, neuromuscular weakness) | Hypoventilation plus another mechanism | Administer oxygen and see if hypoxaemia gets corrected | Reduced FiO2 (high altitude, malfunction of ventilator) |

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                                      ┌──────┴──────────┐
                                   ┌──┴──┐          ┌───┴──┐
                                   │ No  │          │ Yes  │
                                   └──┬──┘          └───┬──┘
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| Shunt (intra-cardiac, intra-pulmonary e.g. atelectasis, pneumoina, congestive heart failure) | Ventilation/perfusion mismatch (asthma, COPD, ILD, pneumonia, ARDS, pulmonary embolism) |

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                              ┌──────────────┐
                              │ Chest X-ray  │
                              └──────┬───────┘
                         ┌──────────┴──────────┐
                    ┌────┴─────┐          ┌─────┴────┐
                    │ Abnormal │          │  Normal  │
                    └────┬─────┘          └─────┬────┘
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| Focal infiltrates | Diffuse infiltrates | Asthma, COPD; pulmonary embolism possible |

| Pneumonia Collapse of lung | Acute respiratory distress syndrome Cardiogenic pulmonary oedema |

Q. What are sleep apnoea syndromes?

- Sleep apnoea is defined as an intermittent cessation of airflow in nose and mouth during sleep.
- Apnoea is defined as cessation of airflow for at least 10 seconds with a drop in oxygen saturation.

- Hypopnoea is a reduction in airflow to less than 30% for at least 10 seconds, which is followed by an EEG arousal from sleep or with a drop in haemoglobin oxygen saturation by at least 4%.
- Sleep apnoea are of two types:
  - Obstructive sleep apnoea (OSA).
  - Central sleep apnoea.

Obstructive Sleep Apnoea (OSA)

- This condition occurs most often in obese middle-aged males.
- Intermittent hypoxaemia leads to sympathetic nervous system overactivity, systemic inflammation and oxidative stress leading to endothelial dysfunction and possibly, metabolic dysfunction.
- Associated with increased cardiovascular and cerebrovascular mortality and morbidity. Some of the cardiovascular conditions include hypertension, coronary heart disease, arrhythmias, aortic dissection, pulmonary hypertension and heart failure. Also increases risk of metabolic syndrome, type 2 diabetes mellitus and non-alcoholic fatty liver disease.

Risk Factors

• Advancing age	• Craniofacial abnormalities (e.g. retrognathia, tonsillar hypertrophy,
• Sex (more common in males)	enlarged tongue or soft palate, inferiorly positioned hyoid bone,
• Obesity	maxillary and mandibular retroposition)
• Smoking and alcohol consumption	• Endocrine diseases (e.g. acromegaly, hypothyroidism)

Pathophysiology and Clinical Features

- During sleep, apnoea follows obstruction of upper airway due to pharyngeal closure.
- When awake, this tendency is overcome by the action of opening muscles of the upper airway—the genioglossus and palatal muscles, which become hypotonic during sleep.
- Many patients commonly have anatomical abnormalities of the upper airway such as increased tongue size or enlarged tonsillar tissue, lateral pharyngeal walls and total soft tissue.
- Apnoea leads to hypoxaemia and increasingly strenuous respiratory efforts until the patient overcomes the resistance. The combination of the effort and the central hypoxic stimulation wakes the patient from sleep. These awakenings are so brief that the patient remains unaware of them.
- This produces deprivation of night-time sleep with consequent daytime sleepiness and impaired intellectual performance.
- Many patients also develop hypertension secondary to chronic hypoxaemia.
- Nocturnal symptoms are sometimes apparent to the patient but generally are reported by a bed partner. Bed partners will report a sudden cessation of snoring followed by a loud snort and the resumption of snoring.
- Pickwickian syndrome (also known as obesity hypoventilation syndrome) represents patients with morbid obesity (BMI >30 kg/m^2) who have chronic sleep-induced central hypoventilation and develop daytime somnolence after ruling out other disorders that may cause alveolar hypoventilation (severe obstructive or restrictive pulmonary diseases, chest wall disorders, neuromuscular diseases, severe hypothyroidism and congenital central hypoventilation syndrome). Many of these patients also have OSA while a few have sleep hypoventilation (an increase of at least 10 mmHg in PaCO$_2$ during sleep). These patients have hypoxaemia (PaO$_2$ <70 mmHg), hypercapnia (PaCO$_2$ >45 mmHg), polycythaemia, pulmonary hypertension and right-sided failure.

Nocturnal features	Daytime features
• Loud snoring	• Daytime sleepiness
• Restless sleep	• Morning headache
• Nocturnal choking	• Hypertension
• Witnessed apnoea	• Pedal oedema (due to pulmonary hypertension)
• Drooling	• Reduced libido
• Gastro-oesophageal reflux	• Xerostomia
• Vivid dreams	• Impaired concentration (increased accidents)
• Nocturia	• Fatigue

Diagnosis

- In many cases, this can be made on the basis of good history supported by pulse oximetry demonstrating fall in oxygen saturation during apnoea. There are severe limitations to this technique, especially the inability to detect apnoeas or hypopnoeas not associated with oxygen desaturation. Furthermore, nocturnal oxygen desaturation may be related to sleep hypoventilation without upper airway obstruction, e.g. COPD, severe kyphoscoliosis, muscular dystrophy. Thus, most patients would require objective assessment and diagnosis by a sleep study using polysomnography. This involves oximetry, direct recordings from thoracic and abdominal muscles to assess breathing, electrocardiogram, electro-oculography (eye movement) and electroencephalography to record the patterns of sleep and arousal. The apnoea–hypopnoea index (AHI) is calculated by the average number of apnoeas and hypopnoeas per hour of sleep. Diagnosis of sleep apnoea is confirmed if AHI ≥5.
  - Mild OSA – AHI 5–15
  - Moderate OSA – AHI 16–30
  - Severe OSA – AHI >30
- Daytime sleepiness can be assessed by various scales. One of the most commonly used scale is Epworth Sleepiness Scale (ESS).
- If AHI of 40 occurs during the first 2 hours, continuous positive airway pressure (CPAP) therapy can then be initiated to determine pressure requirement for treatment purpose. This technique is termed as split-night study (initial diagnostic polysomnography followed by CPAP titration during polysomnography on the same night).

Treatment

- Correction of treatable causes (obesity, acromegaly, hypothyroid, enlarged tonsils or adenoids) and removal of any respiratory depressants (alcohol, and sedatives).
- Avoiding supine sleep may be all that is required in some patients, particularly those with mild apnoea.
- If these fail, the patient should be given CPAP during sleep. CPAP is initiated and titrated to the level required to eliminate all disordered breathing, snoring and flow limitation. CPAP maintains upper airway patency by creating a "pneumatic splint".
- Non-invasive positive pressure ventilation (bilevel nasal positive pressure or BiPAP) if CPAP fails.
- Oral appliances may be useful in some patients. These devices are designed to advance the mandible, thereby pulling the tongue structure forward and opening the pharyngeal airway.
- Surgery (uvulopalatopharyngoplasty) is required in some cases. It increases the pharyngeal lumen by resecting redundant soft tissue.
- Pharmacotherapy:
  - Several drugs including fluoxetine, mirtazapine, protryptyline, clonidine, theophylline, naloxone, doxapram, oxymetazoline nasal application, inhaled nasal corticosteroids, acetazolamide and medroxyprogesterone have been tried. None of them has been shown to produce consistent benefit in patients with OSA.
  - Modafinil, a wake-promoting drug used for treating narcolepsy, has been approved to treat excessive somnolence in adult patients with OSA who are otherwise well with positive airway pressure.

Central Sleep Apnoea

- Characterised by repetitive, complete cessation of airflow and ventilatory effort during sleep (compared with OSA, in which ventilator effort persists).
- Causes are a congenital central sleep apnoea (Ondine's curse) and a variety of neurological lesions leading to failure of respiratory drive. Common mechanisms include:
  - Primary central alveolar hypoventilation syndrome (patients have chronic hypoventilation even during daytime, which gets aggravated during sleep).
    - Unknown aetiology.
    - Probably due to high chemoresponsiveness of the respiratory system so that significant hypoxiaemia and hypercapnia rarely develop during the course of the disease.
    - Apnoeas are terminated with an abrupt and large breath.
    - Daytime somnolence is less common than that in OSA.
  - High altitude.
  - Stroke, tumours and neurodegenerative diseases (e.g. Parkinson's disease and multisystem atrophy).
  - Left ventricular failure:
    - Associated with Cheyne–Stokes breathing.

- Associated with presence of at least 10 central apnoeas and hypopnoeas per hour of sleep in which the hypopnoea has a crescendo–decrescendo pattern of tidal volume accompanied by frequent arousals from sleep.
- Treatment:
  - Administration of oxygen during sleep.
  - Acetazolamide and theophylline may be tried though effect is modest.
  - Nasal CPAP.
  - Non-invasive positive pressure ventilation (bilevel nasal positive pressure) in patients unresponsive to CPAP.
  - Treatment of congestive heart failure.
  - β-blockers useful in central sleep apnoea associated with in congestive heart failure.

Q. What are the common therapeutic indications of oxygen therapy in clinical practice? Add a note on the hazards of oxygen therapy.

Therapeutic Indications

• Pulmonary oedema	• Acute attack of bronchial asthma
• COPD	• ARDS
• Respiratory paralysis	• Anaerobic infections
• To prevent development of severe pulmonary hypertension	• High altitude

Hazards of Oxygen Therapy

- CO_2 narcosis occurs when high oxygen concentrations are administered to patients with ventilatory failure, who are dependent on hypoxic drive, e.g. COPD.
- Idiopathic epilepsy.
- Lung complications:
  - Irritation of respiratory tract
  - Pulmonary oedema
  - ARDS
  - Consolidation
  - Progressive decrease in lung compliance, ultimately leading to fibrosis.
- In premature infants and neonates:
  - Retrolental fibroplasia and blindness
  - Bronchopulmonary dysplasia.

Techniques of Administration

- Fraction of inspired oxygen (FiO_2) while inhaling 100% oxygen depends upon rate of oxygen flow and minute ventilation of patient.

Oxygen Masks

- These are designed to produce a high inspired concentration with FiO_2 varying from 35% to 60% at flow rates of 10-15 L/minute.
- FiO_2 can be controlled using ventimasks where the flow rate is kept constant.
- A non-rebreather mask has an oxygen reservoir and can provide FiO_2 of 95%. It has a one way valve that does not allow rebreathing of exhaled air.

Nasal Cannulae

- Double cannulae fit into the nostrils and do not interfere with eating, drinking and wearing of spectacles. It is particularly useful in long-term oxygen therapy.

- Nasla canula can provide FiO_2 of 25% to 40% depending upon flow rate. A flow rate >4 L/minute is poorly tolerated.

Humidification

- Oxygen is humidified, either by passing it over warm water or through a nebuliser. When masks are used, only humidified oxygen should be used.

Through Endotracheal Tube

- When a patient cannot maintain adequate ventilation using canula and mask, endotracheal intubation is required for administration of oxygen.

Q. Describe acute respiratory distress syndrome (ARDS)

Q. What non-cardiogenic pulmonary oedema?

- Acute respiratory distress syndrome (ARDS) is a serious disease characterised by damage to alveolar epithelium and pulmonary capillary endothelium. Alveolar spaces become flooded with oedema fluid of high protein content. The term 'acute lung injury (ALI)' is no longer used.
- Non-cardiogenic pulmonary oedema is occurrence of pulmonary oedema due to various disorders in which factors other than elevated pulmonary capillary pressure are responsible for protein and fluid accumulation in the alveoli. ARDS is one form of non-cardiogenic pulmonary oedema. Others include high altitude pulmonary oedema, salicylate toxicity, neurogenic pulmonary oedema and re-expansion pulmonary oedema. In practice, terms ARDS and non-cardiogenic pulmonary oedema are used interchangeably.

Definition

Berlin definition

- Onset within one week of a known clinical insult or new/worsening respiratory symptoms
- Partial pressure of arterial oxygen to FiO_2 ratio ≤300 mmHg, irrespective of PEEP
- Bilateral pulmonary infiltrates on chest radiograph not fully explained by effusions, lobar/lung collapse, or nodules
- Respiratory failure not fully explained by cardiac failure or fluid overload; need objective assessment (e.g., echocardiography) to exclude hydrostatic oedema if no risk factor present.

Aetiology of ARDS

- Occurs due to a primary lung disease or secondary to a number of systemic disease processes.

Common causes of ARDS

• Pulmonary infections	Viral, bacterial, fungal, *Pneumocystis jiroveci*, Mycoplasma
• Aspiration	Vomitus, water (near drowning)
• Inhalation	Ammonia, chlorine, nitrogen dioxide, ozone, oxygen, smoke
• Narcotic overdose	Heroin, methadone, morphine, dextropropoxyphene
• Non-narcotic drugs	Barbiturates, thiazides, nitrofurantoin
• Systemic disorders	Shock, sepsis, uraemia, eclampsia
• Blood disorders	DIC, blood product transfusion, thrombocytopenic purpura, massive blood transfusion
• Lung emboli	Fat, air, amniotic fluid
• Miscellaneous	Acute pancreatitis, raised ICP, cardiopulmonary bypass, severe trauma with shock, Goodpasture's syndrome, SLE

Pathophysiology

- Related to altered pulmonary capillary permeability and alveolar diffusion capacity, as well as the increased intra-pulmonary shunt (due to pulmonary vasodilation in non-ventilated lung regions and vasoconstriction in ventilated areas).
- ARDS can be divided into three histopathological phases:
  - Exudative phase (1–3 days) is characterised by diffuse alveolar damage with necrosis of majority of type I pneumocytes, diffuse microvascular injury, and influx of inflammatory cells and proteinaceous fluid into the interstitium. There is a complex inter-relationship between cytokines and pro-inflammatory mediators that initiate and amplify the inflammatory response. The cellular responses include endothelial adhesion molecules expression, as well as margination and migration of neutrophils. Other responses include release of cytokines, lipid mediators, proteases, oxidants, growth factors, nitric oxide and nuclear factor-κB (NF-κB). Coagulation cascade abnormalities are characteristic in ARDS with an imbalance in both pro and anticoagulation factors.
  - Proliferative phase (3–7 days) is characterised by prominent interstitial inflammation and early fibrosis.
  - Fibrotic phase occurs in some cases and is characterised by proliferation of fibroblasts resulting in lung fibrosis.
- Systemic manifestations are frequent due to underlying triggering conditions as well as release of various cytokines [including interleukin-1 (IL-1), IL-6 and tumour necrosis factor (TNF)].
- Multiorgan dysfunction syndrome (MODS) can occur.
- The major pathophysiologic consequence of oedema in patients with ARDS is impaired gas exchange with intrapulmonary shunt, which is manifested as profound hypoxaemia.

Clinical Features

- About 50% patients who develop ARDS do so within 24 hours of the inciting event.
- The earliest sign is tachypnoea, shortly followed by dyspnoea. A few fine inspiratory crepitations may be audible.
- With progression, the patient becomes cyanotic, more dyspnoeic and tachypnoeic. Crepitations are more prominent and heard throughout both lung fields, especially over basal areas. Tubular breath sounds may be heard.
- With further progression, hypotension and worsening of blood gas abnormalities lead to death.

Investigations

- Chest radiography:
  - In early stages, chest radiograph may be normal or may demonstrate minimal scattered interstitial infiltrates.
  - Later, diffuse, extensive bilateral interstitial and alveolar infiltrates appear ("fluffy" or "soft" shadowing). These are located more at the periphery of the lungs.
  - Air bronchograms are more commonly seen as compared to cardiac pulmonary oedema.
  - Cardiac size is normal.
  - Cardiomegaly, bilateral upper lobe vascular diversion and effusions are more suggestive of cardiac failure than ARDS.
- ABG analysis:
  - In the early stages, the only abnormality is mild hypoxaemia (low PaO_2). As the disease progresses, hypoxaemia worsens and hypercapnia appears.
  - In the late stages, there occurs severe hypoxaemia (low PaO_2) and severe hypercapnia (high $PaCO_2$).

Severity of ARDS (Based on PaO2 /FiO2 Ratio)

Severity	Definition
Mild	PaO_2/FiO_2 = >200 to ≤300 mmHg with PEEP or CPAP ≥5 cm of H_2O
Moderate	PaO_2/FiO_2 = >100 to ≤200 mmHg with PEEP ≥5 cm of H_2O
Severe	PaO_2/FiO_2 = ≤100 mmHg with PEEP ≥5 cm of H_2O

- CT scan:
  - Predominant features of ARDS are diffuse consolidation with air bronchograms, bullae, pleural effusions, pneumomediastinum and pneumothorax.
  - Later, lung cysts may be evident.

Management

- Supportive care:
  - Treatment of the underlying cause.
  - Avoiding secondary lung injury such as aspiration, barotrauma, nosocomial infections or oxygen toxicity.
  - Maintaining adequate oxygen delivery to end-organs by minimizing metabolic rate and optimizing cardiovascular function and body fluid balance.
  - Nutritional support.
- Correction of hypoxaemia:
  - Initially, hypoxaemia may be correctable with supplemental oxygen.
  - In most patients, hypoxia is progressive and the patient often requires intubation and mechanical ventilation with low tidal volume (5–7 mL/kg) and positive end-expiratory pressure (PEEP) between 5 and 20 cm of H_2O. This strategy is called lung protective ventilation. PEEP helps in redistribution of capillary blood flow resulting in improved ventilation–perfusion (V/Q) matching, and recruitment of previously collapsed alveoli and prevention of their collapse during expiration.
  - In severe ARDS (PaO2/FiO2 <100 mmHg), ventilation in prone position has been shown to improve oxygenation.
  - While on mechanical ventilator the concentration of inspired oxygen should be kept as low as possible, the goal being maintaining oxygen saturation above 90%.
  - Permissive hypercapnia is a strategy to protect lungs. A gradual and modest increase in $PaCO_2$ (50–75 mmHg) with reasonable degree of acidosis (pH of 7.2–7.3) is achieved by adjusting tidal volume and respiratory rate.
- Optimise systemic perfusion by judicious use of fluids (fluid conservative strategy once shock is corrected), vasopressors, inotropic agents and PEEP.
- Treat pneumonia and other infections.
- Routine stress ulcer prophylactic therapy.
- Role of steroids is controversial. Low-dose glucocorticoid treatment in early ARDS, not persistent ARDS, may be associated with reduction in duration of mechanical ventilation and ICU length stay but with no effect on mortality.
- Experimental therapies:
  - Nitric oxide inhalation as it is a potent vasodilator that improves blood flow to well-ventilated areas.
  - Liquid ventilation by filling the lungs with a perfluorocarbon, a low surface tension fluid with a high affinity for oxygen and CO_2.
  - High frequency ventilation—ventilation at a high rate (180–900/minute).
  - Inverse ratio ventilation (inspiration:expiration ratio of 1:1 to 3:1).
  - Extracorporeal membrane oxygenation of blood—utilising external membranes for oxygenation and removal of CO_2 from blood.

Q. Discuss non-invasive ventilation.

- Mechanical ventilation can be provided either by endotracheal intubation (invasive ventilation) or by a special mask (Non-invasive ventilation).

Non-Invasive Ventilation (NIV)

- A tight-fitting full-face or nasal mask is required.
- Used to deliver either continuous positive pressure ventilation (CPAP) or bilevel positive airway pressure (BiPAP–different levels of positive pressures during inspiration and expiration) ventilation when there is a need

for ventilatory assistance, as indicated by such symptoms as worsened dyspnoea, acute respiratory acidosis and worsened oxygenation.

- CPAP is applied through a face mask or a nasal mask. During CPAP, pressure greater than atmospheric pressure is applied continuously to the airways. Its use averts airway collapse after expiration, thereby maintaining open alveoli. With CPAP, there is no inspiratory muscle unloading; in fact, tidal ventilation is completely dependent on the respiratory muscles. BiPAP, on the other hand, applies a pressure during the inspiratory phase greater than the pressure applied during exhalation. Thus, BiPAP unloads the respiratory muscles and can provide complete respiratory support.
- CPAP is useful in patients with no ventilatory difficulty who require PEEP to support oxygenation. It is also useful in the final stages of weaning when patients are being observed without ventilatory support. It is also used in patients with OSA.
- The patient should be co-operative and medically stable for NIV.
- Common indications include acute exacerbation of COPD, congestive heart failure and obstructive sleep apnoea.

Indications for Non-Invasive Ventilation

- Increased dyspnoea—moderate to severe
- Tachypnoea (>24 breaths per minute in obstructive, >30 breaths per minute in restrictive lung disease)
- Signs of increased work of breathing, accessory muscle use and abdominal paradox
- Acute or acute on chronic ventilatory failure ($PaCO_2$ >45 mmHg, pH <7.35)
- Hypoxaemia (PaO_2:FIO_2 ratio <200 mmHg)

Contraindications for Non-Invasive Ventilation

- Severe hypoxaemia PaO_2:FIO_2 ratio <75)
- Severe acidaemia
- Multiorgan failure
- Upper airway obstruction
- Anatomic abnormalities that interfere with gas delivery (e.g. facial burn and trauma)
- Respiratory arrest
- Cardiac arrest and haemodynamic or cardiac instability
- Uncooperative patient
- Encephalopathy with inability to protect airways and a high risk of aspiration
- Increased risk of aspiration: copious secretions, vomiting or severe gastrointestinal bleeding
- Recent airway or gastrointestinal surgery
- Inability to fit mask

Q. Discuss the aetiology, clinical features, investigations, complications and management of seasonal influenza.

Aetiology

- Influenza viruses type A and type B belong to the group of myxoviruses (RNA viruses).
- Haemagglutinin and neuraminidase are the major antigenic determinants of influenza A viruses. There are 16 haemagglutinin (H1 to H16) and 9 neuraminidase types (N1 to N9).
- Since 1977, the circulating seasonal influenza A strains have been primarily of the H1N1 and H3N2 subtypes.
- Haemagglutinin mediates attachment and entry of the virus into host cells. It is also the main viral target of protective humoral immunity by neutralizing antibody.

- Neuraminidase facilitates the spread of virions in the host and is the target of neuraminidase inhibitors.
- The M2 protein is a transmembrane proton channel protein responsible for acidifying the virion to allow replication.
- Immunity following infection is type-specific and of short duration.
- Minor antigenic changes periodically occur in either the haemagglutinin or the neuraminidase component or both. This phenomenon is called antigenic drift. It introduces viruses that are different enough from preceding strains and previously acquired immunity is not fully effective against them. This "drift" contributes to yearly seasonal epidemics and is the basis for the yearly change in vaccine formulations.
- Antigenic shift results in a virus of distinctly different antigenic character to which most or all of the population is susceptible. Generally, such shifts occur only every few decades and are the basis for influenza pandemics.
- Influenza viruses also infect other species, including birds and pigs. At times, these animal strains infect humans and spread from person to person.
- Influenza B viruses also mutate periodically, but less dramatically; they drift but do not shift and thus are associated with seasonal epidemics but not with pandemics.

Clinical Features

- Incubation period is 1–2 days.
- Clinical manifestations are sudden onset of fever (may be absent in infants, elderly patients, or immunosuppressed patients), headache, generalised aches and pains, anorexia, nausea, vomiting and a harsh unproductive cough. The fauces are hyperaemic and chest is usually clear.
- In uncomplicated cases, the symptoms subside within 3–5 days.

Investigations

- Leucopenia.
- Isolation of virus from nasopharyngeal aspirate.
- Serological tests for specific antibodies.

Complications

- Tracheitis, bronchitis, bronchiolitis and bronchopneumonia (primary influenza pneumonia).
- Secondary bacterial pneumonia.
- Exacerbation of underlying asthma and COPD.
- Myocarditis, worsening of underlying congestive heart failure and coronary artery disease.
- Encephalitis, post-influenzal demyelinating encephalopathy, peripheral neuropathy myositis.
- Post-influenzal asthenia and depression.

Management

- Bed rest till fever subsides.
- Paracetamol 0.5–1 g every 6 hourly.
- Aspirin should be avoided, particularly in adolescents and children, because of its association with the Reye's syndrome.
- In influenza A infection, amantadine (100 mg twice a day) or rimantadine (100 mg twice a day) for 3–5 days reduces the average duration of illness by 1 day. Both are M2 inhibitors. Major side effects include central nervous system adverse effects (confusion, disorientation, mood alterations, memory disturbances, delusions, nightmares, ataxia, tremors, slurred speech, visual disturbances and delirium), gastrointestinal upset and anti-muscarinic effects.
- Oseltamivir and zanamivir (neuraminidase inhibitors) have been approved for the treatment of both influenzae A and B. Both are equally effective in reducing symptoms and duration of illness when taken within 48 hours of the onset of symptoms. Oseltamivir is given in a dose of 75 mg twice a day while zanamivir is administered by oral inhalation of dry powder at a dose of 10 mg twice a day.
- Specific treatment of complications.

Prevention

Vaccination

- Specific vaccination gives 70% protection.
- Two types of vaccines against seasonal influenza are available: trivalent inactivated vaccine (injectable) and live attenuated influenza vaccine (nasal spray). Both vaccines contain three strains of influenza: an H3N2 virus, an H1N1 (seasonal) virus and an influenza B virus. Vaccine composition is adjusted yearly.
- Annual winter vaccination is recommended for patients with chronic pulmonary, cardiac or renal disease.
- Live attenuated influenza vaccine is approved only for healthy non-pregnant persons aged 2 to 49 years. The inactivated vaccine is approved for use in all persons older than 6 months. Both vaccines are produced in a process that uses chicken eggs and allergy to eggs is a contraindication to either vaccine.
- Live attenuated vaccine should not be given to persons with asthma, reactive airways disease or other chronic cardiopulmonary conditions. It is also contraindicated in persons with other medical conditions such as diabetes mellitus, renal dysfunction, haemoglobinopathies or immune deficiency. Other contraindications include pregnant women and those receiving antiviral drugs active against influenza.

Drugs

- Amantadine and rimantadine are useful for prophylaxis of influenza A.
- Oseltamivir and zanamivir are helpful in influenzae A and B prophylaxis.

Q. Discuss briefly about swine flu (H1N1 influenza) and prevention of human influenza panendemic.

- The pandemic of influenza labeled as H1N1 influenza or swine flu was reported for the first time in March 2009 from Mexico and then spread globally. Presently, H1N1 influenza is in post-pandemic phase. Subsequently, the influenza activity in the world has declined.
- Despite its H1N1 designation, the currently circulating strain that seems to have originated in swine (pig) is entirely different from the H1N1 strains of seasonal influenza and thus triggered a pandemic. It has the genetic structure resulting from reassortment of genes from four influenza viruses, i.e. North American swine influenza, Asia/Europe swine influenza, human influenza and avian influenza (non-H5). Reassortment is when 2 or more viruses infect the same host cell and then exchange genes during replication. The new virion has gene segments from each of its parent virus.
- Unlike yearly epidemics during the cold weather months, pandemics may begin and persist during the warmer months. Morbidity and mortality vary depending on the virulence of the pandemic strain and may affect young, healthy individuals. In the present H1N1 pandemic, mortality and morbidity is lower compared to seasonal influenza.
- Although regular flu is most serious in older persons, novel H1N1 seems to affect younger persons more than older persons.
- Currently, H1N1 strain circulates along with typical seasonal influenza viruses and other seasonal influenza viruses within the human population.

Transmission

- Like seasonal influenza, H1N1 is thought to be transmissible by three routes: contact exposure (when a contaminated hand is exposed to facial membranes), droplet spray exposure (when infectious droplets are projected onto mucous membranes) and airborne exposure (via inhalation of infectious airborne particles).
- Unlike other type A influenza viruses that are transmitted by small droplet nuclei, H1N1 virus is usually transmitted by large particle respiratory droplets and hence requires a less than 6 feet distance between the source and the susceptible individual to be present for effective spread.
- The possibility of indirect transmission from fomites and contaminated surfaces is possible and therefore, all body fluids (e.g. stool and respiratory secretions) are potentially infectious.
- Infected persons start shedding virus 1 day before the onset of symptoms and shed it at least until symptoms resolve. Children and younger adults may shed the virus for as long as 10 or more days and immunosuppressed persons may shed the virus for weeks.

Clinical Features

- The incubation period for the H1N1 virus has been estimated to be between 1 and 7 days, similar to that of seasonal influenza.
- Usually patients present with a mild disease characterised by fever (at least 100.4° F), cough and myalgias.
- Watery diarrhoea is common in H1N1 infection.
- Most patients recover with symptomatic treatment.
- Some cases may develop severe, rapidly progressive course. These patients develop dyspnoea, cyanosis, haemoptysis, chest pain, confusion and hypotension. Ventilatory support is often required in these patients.

Complications

- Similar to those of seasonal influenza (mentioned above).

Groups at High Risk of Influenza-Related Complications

- Children <5 years
- Adults ≥65 years
- Women who are pregnant or postpartum (within 2 weeks after delivery)
- Persons with certain chronic medical conditions (asthma, COPD, cardiac, haematologic, hepatic, neurologic and metabolic diseases)
- Immunosuppressed patients
- Adolescents <19 years receiving long-term aspirin therapy

Diagnosis

Case Definitions

- These are utilised for reporting purpose.
- A suspected case of H1N1 virus infection is defined as a person with acute febrile respiratory illness (fever ≥38°C) with onset:
  - within 7 days of close contact with a person who is a confirmed case of H1N1 influenza virus infection, or
  - within 7 days of travel to areas where there are one or more confirmed H1N1 influenza cases, or
  - resides in a community where there are one or more confirmed H1N1 influenza cases.
- A probable case of H1N1 influenza virus infection is defined as a person with an acute febrile respiratory illness who:
  - is positive for influenza A, but unsubtypable for H1 and H3 by influenza real time-polymerase chain reaction (RT-PCR) or reagents used to detect seasonal influenza virus infection, or
  - is positive for influenza A by an influenza rapid test or an influenza immunofluorescence assay (IFA) plus meets criteria for a suspected case, or
  - individual with a clinically compatible illness who died of an unexplained acute respiratory illness who is considered to be epidemiologically linked to a probable or confirmed case.
- A confirmed case of H1N1 influenza virus infection is defined as a person with an acute febrile respiratory illness and with laboratory confirmed H1N1 influenza virus infection by one or more of the following tests:
  - RT-PCR, or
  - Viral culture or
  - Four-fold rise in H1N1 virus-specific neutralising antibodies.

Diagnostic Tests

- For diagnosis of H1N1 influenza infection, respiratory specimen would generally need to be collected within the first 4 to 5 days of illness. However, some persons, especially children, may shed virus for 10 days or longer.
- Preferred respiratory samples include nasopharyngeal swab or aspirate, or oropharyngeal swab. In intubated patients, endotracheal aspirates or bronchoalveolar lavage (BAL) should be obtained.

- Clinical samples should be transported on dry ice.
- Available laboratory tests include:
  - Rapid antigen tests: not as sensitive as other available tests; does not differentiate between various types of influenza A viruses. Detect influenza viral nucleoprotein antigen and can provide results within 30 minutes.
  - Real-time reverse transcription PCR.
  - Virus isolation.
  - Four fold rise in H1N1 influenza virus specific neutralising antibodies.
  - Other tests: Haematological and biochemical testing may suggest leucopenia, elevated lactate dehydrogenase and creatine kinase.
  - Chest X-ray abnormalities may be noted in seriously ill patients.

Treatment

Drug Therapy

- Drug resistance to amantadine and rimantadine has been reported widely and these agents are not recommended for H1N1 influenza.
- Oseltamivir and zanamivir, which inhibit viral release from cells are effective, but only if these agents are used during the first 48 hours of illness. However, treatment is generally well tolerated and even if started late, may improve outcome in critically ill or high-risk patients.
- Oseltamivir is recommended at a dosage of 75 mg twice daily for 5 days (for treatment) or 75 mg daily for 7–10 days (for post-exposure prophylaxis). It can cause nausea and vomiting, rarely confusion, hallucinations and self-injury.
- Zanamivir is recommended at 2 inhalations (10 mg) twice a day for similar periods. It is approved only for those without underlying pulmonary or cardiovascular disease.
- Peramivir, another neuraminidase inhibitor, is under clinical trials. It is given intravenously and may be useful for seriously ill patients.

Supportive Therapy

- Intravenous fluids.
- Parentral nutrition.
- Oxygen therapy/ventilatory support.
- Antibiotics for secondary infection.
- Vasopressors for shock.
- Paracetamol for fever, myalgia and headache.
- Avoid smoking.
- For sore throat, short course of topical decongestants, saline nasal drops, throat lozenges and steam inhalation.
- Aspirin is strictly contraindicated in any influenza patient due to its potential to cause Reye's syndrome.

Prevention

General Measures

- Avoid close contact with people who are having respiratory illness.
- Sick persons should keep distance from others. When the ill person is within 6 feet of others at home, the ill person should wear a face mask, if available or handkerchief or tissues.
- Persons who develop influenza-like-illness (fever with either cough or sore throat) should be strongly encouraged to stay at home for 7 days after the onset of illness or at least 24 hours after symptoms have resolved, whichever is longer. Such persons should contact their healthcare providers to report illness by telephone or other remote means before seeking care at a clinic or hospital. If ill persons must go into the community (e.g. to seek medical care), they should wear a face mask to reduce the risk of spreading the virus in the community. If a face mask is unavailable, ill persons needing to go into the community should use a handkerchief or tissues to cover any coughing and sneezing.
- Cover your mouth and nose with a tissue or handkerchief when coughing or sneezing.
- If tissue or handkerchief is not available, avoid cleaning the nose with hands; instead clean with the cuff of shirt or clothes.
- Frequent washing of hands with soap or alcohol-based hand wash (containing at least 60% alcohol) is recommended. Meticulous hand washing remains the cornerstone of effective infection control. Hands should be washed with soap and

water for 20 seconds or more or rubbed with alcohol gel, paying close attention to technique to ensure all areas of the hands and forearms are clean. Areas commonly missed are the web spaces and fingertips.

- Persons who have difficulty breathing or shortness of breath should seek immediate medical attention and report to the nearby hospital.
- Household contacts who are well should remain at home at the earliest sign of illness.
- Healthcare workers who are likely to come in contact with influenza patient should use N95 particulate respirator masks.

Drug Prophylaxis

Indications

- All close contacts of patients need drug prophylaxis. Close contacts include household/social contacts, workplace or school contacts, who had contact with patient at a distance below 6 feet.
- All healthcare personnels coming in contact with suspected, probable or confirmed cases.

Drugs and Dosage

- Oseltamivir is the drug of choice. Prophylaxis provided till 10 days after last exposure (maximum period of 6 weeks). Dose is:
  - Infants <3 months — not recommended
  - Infants 3–5 months: 20 mg OD
  - Infants 6–11 months: 25 mg OD
  - Above 1 year of age:
    - Weight <15 kg: 30 mg OD
    - Weight 15–23 kg: 45 mg OD
    - Weight 24–40 kg: 60 mg OD
    - Weight ≥40 kg: 75 mg OD.

Vaccines

- Egg-based, inactivated and live attenuated vaccines (used intranasally) are available in India.
- Inactivated vaccines can be used in person above age of 6 months. It is not given if person is allergic to eggs.
- Live attenuated vaccine is for people in the age group 3–50 years and is not meant for pregnant women and those with immunocompromised condition.
- Pandemic influenza vaccines are not expected to provide protection against other influenza viruses.
- The vaccine becomes effective approximately 14 days after vaccination.
- Groups considered to be high priority to receive prophylactic vaccination with inactivated vaccine are given in the box.

- Pregnant women (because they are at higher risk of complications and can potentially provide protection to infants who cannot be vaccinated)
- Household contacts and caregivers for children <6 months of age (because younger infants are at higher risk of influenza-related complications and cannot be vaccinated. Vaccination of those in close contact with infants <6 months old might help protect infants)
- Healthcare and emergency medical services personnel (because they are at high risk for acquiring infection and can also be a potential source of infection for vulnerable patients. Also, increased absenteeism in this population could reduce healthcare system capacity)
- All people from 6 months through 24 years of age
  - Children from 6 months through 18 years of age (because they are in close contact with each other in school, college and daycare settings that increases the likelihood of disease spread)
  - Young adults 19 through 24 years of age (because they often live, work and study in close proximity, and they are a frequently mobile population)
- Persons aged 25 through 64 years who have health conditions associated with higher risk of medical complications from influenza (cardiovascular disease, pulmonary diseases, diabetes, liver and kidney diseases, imunosuppressed individuals)

Q. Briefly discuss about avian influenza.

- A primary public health concern of the 21st century.
- Historically, several harmful influenza pandemics have originated from avian influenza viruses through genetic re-assortment between human and avian influenza strains.
- Implicated strains of avian influenza at present include H5N1 and H7N9.
- Avian influenza viruses can be transmitted from their natural reservoir (ducks) to domestic poultry and subsequently to humans.
- Initially H5N1 was reported from China and Hong Kong, but later human cases have been recorded from other parts of the world. H7N9 was reported from China in 2013
- Mortality in humans is as high as 50% of the infected patients.

Mode of Transmission

- Avian influenza A virus is shed in the faeces of healthy-appearing waterfowl (primarily ducks).
- This infects chickens and other poultry with which they come in contact (faeco-oral transmission).
- Mortality rates in chickens and other birds are high.
- Humans get infected primarily after direct contact of infectious secretions or excreta from infected birds or contaminated poultry products. The main infectious routes are via the upper respiratory tract and conjunctive. In addition, gastrointestinal tract remains a possible means of entry. Eating cooked poultry poses no risk.
- Conditions for transmission and jumping species barriers often are ideal in Asia, where poultry, ducks, pigs and humans live in crowded conditions.

Clinical Features

- History of exposure to infected birds is expected because sustained human-to-human transmission in community setting is not yet known to occur. Transmission can occur in healthcare setting.
- Symptom onset usually 2–5 days after exposure (longer than with human influenza infection).
- Characterised by fever (at least 100.4° F), cough, rhinorrhea and myalgias.
- Watery diarrhoea is fairly common particularly with H7N9 virus. Patients may also develop abdominal pain and vomiting.
- Usually followed by viral pneumonia with increasing respiratory distress and ARDS. Ventilatory support is often required. Mortality may be as high as 50%.

Investigations

- Leucopenia, thrombocytopenia.
- Elevated levels of hepatic aminotransferase, lactate dehydrogenase and creatine kinase.
- Chest X-ray shows infiltrates around 7 days after the onset of fever. Other findings may include lobar collapse and focal consolidation.
- Diagnosis is made by viral isolation or detection of H5-specific RNA. Pharyngeal swabs and specimens from lower respiratory tract are preferred for the diagnosis over nasal swabs because avian viral titres are greater in the throat and lower respiratory tract. Reverse transcriptase polymerase chain reaction (RT-PCR) assays are more sensitive in detecting H5N1 than commercial rapid antigen tests.

Prevention and Treatment

- Avoid live animal markets and poultry farms in case of an outbreak.

Drug Treatment

- Similar to H1N1 influenza.

Non-Pharmacologic Approaches

- These include the influenza surveillance for early warning, travel restrictions, quarantine, use of N95 particulate respirator masks, communications networking and international teamwork to cordon off the infected areas.
- Proper poultry-handling practice and personal hygiene (such as handwashing) and minimizing contact with birds are basic precautions that must be enforced during an outbreak.

Q. Write a short note on severe acute respiratory syndrome (SARS).

- Severe acute respiratory syndrome (SARS) was described for the first time in 2002 from Southern China and rapidly spread to several countries within less than a year. More than 8000 probable cases were reported in 29 regions with a death rate of nearly 10%. Presently, it has not been reported from any country. But given the possibility that human or animal reservoirs of the virus may still exist, there is concern that SARS may return.
- A novel coronavirus (SARS CoV) has been identified as the pathogen responsible for SARS. It is not closely related to any of the previously characterised coronaviruses.
- Spreads by close person-to-person contact via droplet transmission or fomite.

Clinical Features

- Incubation period 2–10 days, but may be as long as 16 days.
- Presents as prolonged influenza-like illness with persistent fever, chills/rigor, myalgia, malaise, dry cough, headache and dyspnoea. Less common symptoms include sputum production, sore throat, rhinorrhoea, nausea, vomiting and diarrhoea.
- 20% of patients developed evidence of ARDS over a period of 3 weeks.
- Older subjects may present with decrease in general wellbeing, poor feeding, fall and in some cases, delirium, without the typical febrile response.

Laboratory Investigations

- Lymphopenia occurs due to the destruction of both CD4 and CD8 lymphocytes.
- Features of low-grade disseminated intravascular coagulation (DIC) (thrombocytopenia, prolonged activated partial thromboplastin time and raised D-dimer).
- Elevated lactate dehydrogenase, liver transaminases and creatine kinase.
- Chest X-ray:
  - Predominant involvement of lung periphery and the lower zone, and absence of cavitation, hilar lymphadenopathy or pleural effusion.
  - Lesions progress from unilateral opacity to either multifocal or bilateral involvement.
  - Spontaneous pneumomediastinum in some patients.
  - Normal chest X-ray in about 25%.
- Confirmation:
  - Detection of SARS CoV in urine, nasopharyngeal aspirate and stool specimen using RT-PCR.
  - Quantitative measurement of SARS CoV RNA in blood with RT-PCR technique.
  - Viral culture.

Treatment

- Supportive treatment includes fluid and electrolyte balance, oxygenation and if required, ventilation with proper protection of healthcare workers.
- High-dose methylprednisolone (0.5 g daily) is given if pneumonia or hypoxaemia develops.
- Interferon-α may be combined with steroids.
- Ribavirin or lopinavir/ritonavir, as the initial treatment option reduces mortality and intubation rates.

Write a short note on Middle East respiratory syndrome (MERS).

- Caused by a novel coronavirus (MERS-CoV).
- Most cases have occurred within the Arab Peninsula and neighboring countries with more than 70% from Saudi Arabia.
- Human-to-human transmission can occur although spread may not be efficient. Unlike severe acute respiratory syndrome (SARS) coronavirus, MERS-CoV does not preferentially infect health care workers.
- Transmission occurs more readily if the patient is immunocompromised or has a comorbidity such as diabetes.
- Incubation period 2–14 days (mean 5.2 days).
- Clinical features include flu-like symptoms like cough and fever, followed by lower respiratory tract involvement and ARDS. Some patients may develop abdominal pain, vomiting and diarrhoea. Renal failure has also been commonly reported.
- Leucopenia, thrombocytopenia; elevated liver enzymes, LDH and creatine kinase.

- Chest X-ray shows unilateral or bilateral infiltrates or consolidation.
- Mortality ~50%.
- Diagnosis by RT-PCR.
- Treatment is symptomatic. No drug has been shown to be effective in reducing severity.

Q. Discuss the aetiology, classification, investigations, complications, indications for hospitalisation and treatment of pneumonia.

Q. Describe suppurative pneumonias and necrotizing pneumonias.

Definition

- Pneumonia is defined as inflammation with exudative solidification of the lung parenchyma, generally acute. The term "pneumonitis" is synonymous but is best avoided.

Classification

- Pneumonias can be classified in a number of ways. Three classifications are given below.

A. Classification by Site

Alveolar or air space pneumonia or lobar pneumonias
- The organism causes an inflammatory exudate that involves many contiguous alveoli. Segmental boundaries are not preserved and the bronchi remain patent. This results in a radiographic appearance of non-segmental consolidation with air bronchograms. The typical example is pneumococcal pneumonia

Interstitial pneumonia
- The inflammation is confined to interalveolar septa. Radiographically, it gives a reticular pattern. *Mycoplasma pneumoniae, Pneumocystis jiroveci* and viruses cause interstitial pneumonia

Bronchopneumonia
- Inflammation is restricted to the conducting airways, especially terminal and respiratory bronchioles, and the surrounding alveoli. Radiographically, atelectasis may be present and air bronchograms are absent
- The typical example is staphylococcal pneumonia

B. Classification by Aetiology

- Pneumonias can also be classified into primary, secondary and suppurative pneumonias.

Primary Pneumonia

- Primary pneumonia is caused by a specific pathogenic organism. There is no pre-existing abnormality of the respiratory system. The organisms causing primary pneumonia are given below.

Common	Less common
• *Streptococcus pneumoniae* (most common)	• *Klebsiella pneumoniae*
• *Haemophilus influenzae*	• *Streptococcus pyogenes*
• *Moraxella catarrhalis*	• *Pseudomonas aeruginosa*
• *Staphylococcus aureus*	• *Coxiella burnetii (Q fever)*
• *Legionella pneumophila*	• *Chlamydophila pneumoniae or Chlamydia pneumoniae*
• *Mycoplasma pneumoniae*	• *Chlamydophila psittaci*
	• Viruses: H1N1 influenza virus, seasonal influenza virus, corona virus producing severe acute respiratory syndrome (SARS)
	• *Actinomyces israeli*

- The term "atypical pneumonia" has been used to describe pneumonia caused by agents such as Mycoplasma, Legionella, Chlamydophila and Coxiella. Though there are a few symptoms that help in differentiating pneumonia caused by these organisms from pneumococcal pneumonia, there is a considerable overlap in the clinical presentation.

Secondary Pneumonia (Including Aspiration Pneumonia)

- Secondary pneumonia (aspiration pneumonia) is characterised by the absence of any specific pathogenic organism in sputum and the presence of some pre-existing abnormality of respiratory system. The pre-existing abnormality of the respiratory system predisposes to the invasion of the lung by organisms of low virulence derived from upper respiratory tract or oropharynx.
  - Aspiration of pus from infected nasal sinuses.
  - Inhalation of septic matter during tonsillectomy or dental extraction under general anaesthesia.
  - Vomitus or the contents of a dilated oesophagus may enter the larynx and could be aspirated during general anaesthesia, coma or even sleep.
  - Aspiration of gastric contents in patients with gastro-oesophageal reflux disease (GERD).
  - In acute bronchitis, bronchiectasis and lung abscess, pus may be carried into the alveoli.
  - Ineffective coughing (post-traumatic, post-operative) and laryngeal paralysis predispose to aspiration.
  - Partial bronchial obstruction (e.g. by a tumour) causes stasis of secretions and secondary infection distal to the site of obstruction.

Suppurative Pneumonia (Necrotising Pneumonia)

- In most pneumonias (primary and secondary), with successful inactivation of the organism, complete resolution occurs and normal lung structure is restored. In some cases, complete healing does not occur. Here, the prominent features are destruction of lung tissue by inflammation, abscess formation and subsequent development of fibrosis and bronchiectasis. The term suppurative pneumonia (necrotizing pneumonia) has been applied to this group of conditions.
- Causative organisms include *S. aureus, Klebsiella pneumoniae* and occasionally, *H. influenzae* and *S. pneumoniae*.

C. Classification by Mode of Acquiring Pneumonia

Community-Acquired Pneumonia (CAP)

- It indicates pneumonia occurring in a person in a community (outside hospital). It is defined as an acute pulmonary infection in a patient who is not hospitalised or living in a long-term care facility 14 or more days before presentation and does not meet the criteria for health care associated pneumonia (HCAP).
- The most common organisms producing CAP are *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Legionella sp.* (Legionnaire's disease), *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*. The first three organisms account for nearly 85% of all cases of CAP. This fact is important for selecting an antibiotic for treatment.
- This category includes both immunocompetent and immunocompromised patients as causative organisms are almost similar in both the cases.

Nosocomial Pneumonia or Hospital-Acquired Pneumonia

- Nosocomial pneumonia indicates the development of pneumonia after more than 48 hours of hospitalisation.
- Majority of cases of nosocomial pneumonia occur outside intensive care units. However, the highest risk is in the patients on mechanical ventilation [ventilator-associated pneumonia (VAP)].

Pneumonia in Immunocompromised Host

- Seen in immunocompromised patients like neutropenic patients, patients with HIV infection and malignancies and patients on immunosuppressives.
- May be caused by classical organisms, atypical organisms, *Mycobacterium tuberculosis* or *Pneumocystis jiroveci*.
- Symptoms are usually more than the signs.

Health Care Associated Pneumonia (HCAP)

- Defined as infection occurring within 90 days of a 2 day or longer hospitalisation; stay in a nursing home or long-term care residence in last 30 days; within 30 days of receiving intravenous antibacterial therapy, chemotherapy, or wound care or after a hospital or haemodialysis clinic visit; or in any patient in contact with a multidrug-resistant pathogen.
- Patients with HCAP more closely resemble patients with nosocomial pneumonia and may require treatment accordingly.

Pathological Stages in Development of Pneumonia

- Four stages; all stages may be seen at the same time in different areas:
  - Stage of congestion—just congestion of the vessels without alveolar exudation; fine crepitations may be heard
  - Stage of red hepatisation—intra-alveolar exudation especially with RBCs; tubular bronchial breathing heard
  - Stage of grey hepatisation—the exudation is of mainly WBCs with minimal RBCs; tubular bronchial breathing heard
  - Stage of resolution—the exudate is absorbed or removed by macrophages & proteolytic enzymes; coarse crepitations heard

Clinical Features

History

- Classical features of CAP are sudden onset of rigors followed by fever, pleuritic chest pain, cough productive of purulent sputum and haemoptysis.
- These symptoms may be absent in elderly patients who present with confusion.
- Patients with atypical pneumonia may have a dry cough. These patients often have extrapulmonary features that include myalgias, arthralgias, prominent headache, mental confusion, abdominal pain and diarrhoea. Haemoptysis is uncommon in atypical CAP.

Examination

- Approximately 80% are febrile, although this finding is frequently absent in older patients.
- Respiratory rate is high and this may be the most sensitive sign in the elderly.
- Tachycardia is common. However, relative bradycardia is a typical feature of Legionnaire's disease.
- Chest examination reveals crepitations in the involved area. About one-third have bronchial breathing.

Investigations

- Total and differential leucocyte count: Leucocytosis with a high percentage of polymorphonuclear leucocytes suggest bacterial pneumonia. In viral and atypical pneumonias, total leucocyte count is often less than 5000/mm^3.
- Blood culture: This may grow the causative organism, particularly in pneumococcal pneumonia. However, blood cultures are recommended only in hospitalised patients.
- Respiratory secretions: Respiratory secretions should be subjected to microscopic examinations as well as culture. These are recommended only in hospitalised patients. Microscopic examination should include Gram staining and Ziehl–Neelsen staining. Culture (including anaerobic culture when indicated) and sensitivity testing should be done. A freshly obtained specimen of expectorated sputum is the ideal. An ideal sputum specimen can be distinguished from saliva by microscopic examination. An ideal sputum specimen from the lower respiratory tract will have polymorphonuclear leucocytes and alveolar macrophages, but very few oral squamous epithelial cells (a sputum specimen that has more than 25 polymorphonuclear neutrophils and less than 10 epithelial cells per low power field represents a purulent specimen). If a patient is not able to expectorate, one of the following methods should be employed:
  - Attempt to induce sputum production by the administration of nebulised hypertonic saline.
  - Percutaneous transtracheal aspiration of secretions.

- Fibreoptic bronchoscopy with BAL and brushings. A transbronchial biopsy of the lung tissue for culture and histology may be done in selected cases.
  - Percutaneous transthoracic needle aspiration, preferably under CT guidance.
- Serological and antigen detection tests: Pneumococcal antigens can be detected in the serum or urine in pneumococcal pneumonia. A four fold rise in antibody titre over 10 days is useful in diagnosing recent infection by mycoplasma, chlamydia, legionella and viral infections.
- Radiological studies: Chest radiograph is essential for the confirmation of diagnosis, follow-up and detection of complications like parapneumonic effusion and empyema. For the radiological features of various types of pneumonias refer classification of pneumonias. Diagnosis of parapneumonic effusion is discussed under pleural effusion.
- Oxygen saturation using a pulse oximeter in patients who are to be managed on outpatient basis.
- ABG analysis: The PaO_2, $PaCO_2$ and H^+ concentration levels are important in the management of seriously ill patients.
- Hyponatraemia, elevated liver enzymes and microscopic haematuria may occur in patients with Legionnaire's disease.
- C-reactive protein and procalcitonin may help distinguish between bacterial and non-bacterial pneumonia. CRP may also be elevated in patients with viral infections, although often not to the same extent as in bacterial infection.

Complications of Pneumonia

- These include parapneumonic effusion, meningitis, arthritis, endocarditis, pericarditis, peritonitis, empyema, septicaemia and ARDS.
- Cavitation or abscess formation occurs in any severe pneumonia, but is more common in *S. aureus*, *Klebsiella* and aspiration pneumonia.
- Pneumothorax, especially in *Staphylococcus* pneumonia.
- Mortality rate of patients who require admission to hospital averages 12% overall but increases to 30–40% for those with severe CAP who require admission to intensive care unit.

Indications for Hospitalisation

Age over 65	Signs
Underlying diseases	- Respiratory rate >30/minute
- Diabetes	- Systolic blood pressure <90 mmHg
- Renal failure	- Diastolic blood pressure <60 mmHg
- Congestive heart failure	- Evidence of extrapulmonary involvement (meningitis, arthritis, etc.)
- Chronic lung disease	
- Alcoholism	**Laboratory parameters**
- Immunosuppression	- White blood cell count <4000 or >30,000/mm³
- Post-splenectomy	- PaO_2 <60 mmHg on room air
- Malignancy	- Renal failure
Altered mental status	- Haematocrit <30%
	- Multilobar involvement on chest X-ray

- The above may also be considered as bad prognostic features.
- The need to hospitalise a patient can also be decided using Pneumonia Severity Index (PSI), which combines several clinical and laboratory features and co-morbid conditions, or CURB-65 (Confusion, Urea concentration >40 mg/dL, Respiratory rate ≥30/minute, Blood pressure with systolic <90 mmHg or diastolic ≤60 mmHg, and age >65) score. Each parameter is assigned one point to get a severity score. The recommendations on the basis of CURB-65 scoring are: outpatient treatment for patients with a score of 0–1, hospital admission for a score of 2 and consideration for admission to ICU with a score of 3 or more.

Treatment

General Measures

- Check the airway, breathing and circulation.
- Treat shock with intravenous fluids initially.

- Correct hypoxia with oxygen inhalation. If hypoxia continues or patient develops increasing hypercapnia, ventilate the patient mechanically.
- Treatment of pleuritic pain with mild analgesics like paracetamol or codeine.

Antimicrobial Therapy

Empiric Regimens

- Administer antibiotics as soon as feasible once the diagnosis of CAP is established.
- Empiric therapy for CAP is based on providing coverage against the most likely pathogens responsible for CAP.
- The antibiotic selected should therefore be active against common typical and atypical pathogens, unless one can clinically differentiate these organisms.
- Macrolides (erythromycin, clarithromycin and azithromycin) should not be used alone in moderately sick patients with CAP since nearly 25% of strains of S. pneumoniae are naturally resistant to macrolides.
- Newer fluoroquinolones like levofloxacin, moxifloxacin and gemifloxacin have better gram-positive coverage than ciprofloxacin. These are effective against both typical and atypical pathogens and can be used as monotherapy, particularly if the patient is not severely ill. However, their use should be restricted as tuberculosis is always a possibility in patients with pneumonia and use of fluoroquinolones may produce partial response and lead to resistance of tubercular bacilli to these agents.
- Ceftriaxone has no activity against atypical pathogens and should not be used alone in moderately sick patients.
- Doxycycline remains effective against both typical and atypical pathogens and is an effective choice in patients with CAP.
- Daptomycin is not effective for MRSA pneumonia because it is inactivated by pulmonary surfactant.
- The approach for empiric antibiotics is shown below. For pneumonia due to typical organisms without an underlying co-morbidity, the usual duration of therapy is 5–7 days. For Mycoplasma and Chlamydia pneumonia, and immunocompromised patients, the duration is 10–14 days. Patients initially treated with intravenous antibiotics can be switched to oral agents when afebrile.

Type of pneumonia	Antibiotic treatment
- Uncomplicated pneumonia; patient not requiring hospitalization	Erythromycin 500 mg 6 hourly orally alone or in combination with cefuroxime or amoxycillin Use clarithromycin or azithromycin if patient is intolerant to erythromycin Consider fluoroquinolone (levofloxacin 750 mg once a day or moxifloxacin 400 mg once a day or gemifloxacin 320 mg once a day) Doxycycline 100 mg 12 hourly Other alternatives: amoxycillin/clavulanate, cefixime, cefpodoxime, cefprozil
- Moderately sick patients requiring hospitalization	Ceftriaxone 2 g once a day IV or cefotaxime (1–2 g 8 hourly) and erythromycin (500 mg 6 hourly) or azithromycin (500 mg once a day) Amoxycillin–clavulanic acid plus erythromycin or azithromycin Fluoroquinolones alone
- Severely sick patients	Ceftriaxone (β-lactam) 2 g once a day IV PLUS either azithromycin 500 mg IV once a day or levofloxacin 750 mg IV once a day If allergic to β-lactam, replace ceftriaxone with aztreonam If methicillin-resistant S. aureus (MRSA) is suspected[#], add vancomycin or linezolid to the above regimens

Type of pneumonia	Antibiotic treatment
• Underlying diseases* (patient sick)	Piperacillin plus tazobactam or cefepime or a carbapenem (meropenem or imipenem/cilastatin) or ceftazidime plus • a fluoroquinolone (including ciprofloxacin), or • aminoglycoside (amikacin or tobramycin) plus azithromycin or clarithromycin, or • aminoglycoside plus fluoroquinolone

#Prior influenza-like illness, necrotising severe pneumonia or if a sputum Gram's stain shows gram-positive cocci in clusters
*Bronchiectasis, use of steroids, repeated exacerbations of COPD, malnutrition, antibiotics for >7 days within 1 month increase risk of infection by Pseudomonas

Risk Factors for Antibiotic Resistance

- Age (either >65 years or <5 years).
- Alcoholism.
- Child attending a day care centre.
- Multiple co-morbidities.
- Prior exposure to an antimicrobial within last 3 months.

Unresolved Pneumonia

- Indicates persistent consolidation despite initial antibiotics and passage of more than 6 weeks.
- Important causes are:
  - Incorrect diagnosis (e.g. neoplasm, pulmonary embolism, systemic vasculitis and eosinophilic pneumonia)
  - Incorrect microbiological diagnosis (e.g. tuberculosis instead of classical organisms)
  - Bronchial obstruction causing partial or complete obstruction
  - Immunocompromised state
  - Nosocomial superinfection.
- Further evaluation in form of microbiological tests for the aetiological agent, CT chest, bronchoscopy, biopsy and other tests are required.

Recurrent Pneumonia

- A number of conditions can produce recurrent pneumonias:
  - Bronchial obstruction (e.g. foreign body, bronchial stenosis, compression of bronchus, endobronchial lesions)
  - Bronchiectasis
  - Sequestration of lung
  - Immunocompromised state
  - Ciliary dyskinesia
  - Multiple myeloma and other lymphoreticular malignancies.

Q. Discuss the aetiology, clinical features, diagnosis, complications and management of pneumococcal pneumonia (lobar pneumonia).

Aetiology

- It is the most common form of pneumonia and the causative organism is *Streptococcus pneumoniae* (i.e. pneumococcus, a Gram-positive, lancet-shaped diplococcus).
- The disease spreads by droplet infection.

Pathology

- Pneumococcal pneumonia is characterised by homogeneous consolidation of one or more lobes or segments. There are four stages in the natural course of the illness:
  1. Stage of congestion
  2. Stage of red hepatisation
  3. Stage of grey hepatisation
  4. Stage of resolution.

Risk Factors for Pneumococcal Pneumonia

- Younger than 2 years or older than 65 years
- Poverty and overcrowding
- Asplenia or hyposplenia
- Alcoholism
- Diabetes mellitus
- Antecedent influenza
- Defects in humoral immunity (complement or immunoglobulin)
- HIV infection
- Severe liver disease
- Chronic lung disease

Clinical Features

- Onset is often sudden with fever, chills and rigors, and vomiting. Convulsions may occur in children. Fever is usually high grade (39–40°C).
- Non-specific symptoms include loss of appetite, headache and aching pains in the body and limbs.
- Localised pleuritic chest pain develops at an early stage. It may be referred to the shoulder or abdominal wall.
- Cough is initially short, painful and dry, but soon becomes productive.
- Sputum is characteristically rust coloured ("rusty" sputum), but occasionally frankly blood stained.
- Breathing is rapid and shallow due to pleuritic pain.
- Other features are tachycardia, hot and dry skin, herpes labialis, flushed face and occasionally, central cyanosis.

Physical Signs in the Chest

- In the first 2 days, physical signs are minimal. These include diminished respiratory movements, slight impairment of percussion note and pleural rub.
- Later, frank signs of consolidation appear. These include the following:

Signs of Consolidation

- No mediastinal shift, diminished respiratory movements, dull percussion note, markedly increased vocal fremitus and vocal resonance, and high-pitched tubular bronchial breathing. Bronchophony, aegophony and whispering pectoriloquy may be present. In early stages, numerous fine crepitations are audible, but later (during resolution) they become coarse
- If parapneumonic effusion develops, additional signs of pleural effusion appear

Investigations

- Marked neutrophil leucocytosis.
- Blood culture may show *Streptococcus pneumoniae.*
- Gram staining of the sputum may demonstrate pneumococci as Gram-positive and lancet-shaped diplococci.
- Sputum culture may show *Streptococcus pneumoniae.*

- Chest radiograph shows a homogeneous opacity localised to the affected lobe or segment, with air bronchograms.
- Associated parapneumonic effusion or empyema can be detected.
- Serological tests can detect pneumococcal antigen in serum, urine and sputum:
  - In urine, C-polysaccharide (part of pneumococcal cell wall) by an immunochromatography assay is quite sensitive. Urinary antigen remains positive for weeks after onset of severe pneumococcal pneumonia. However, it is often negative in mild infections.
  - Assays on sputum are based on detecting nucleic acids for pneumococci. However, these assays do not differentiate between colonisation and infection.
- In rare cases; fibreoptic, bronchoscopic aspiration or transthoracic needle aspiration is required.

Complications

Pulmonary	Pleural
- Delayed/incomplete resolution	- Sterile pleural effusion
- Spread to other lobes (rare)	- Empyema
- Necrotising pneumonia	**Neurological**
Cardiovascular	- Mental confusion
- Acute circulatory failure	- Meningism
- Acute pericarditis	- Meningitis (rare)
- Endocarditis (rare)	

Treatment

General Measures

- Oxygen in high concentrations should be administered to all hypoxaemic patients.
- Treatment of pleuritic pain with mild analgesics like paracetamol. However, some patients require pethidine 50–100 mg or morphine 5–10 mg intramuscularly or intravenously.
- Assisted coughing in patients who suppress cough because of pleuritic pain.

Antibiotic Therapy

- If patient is not seriously ill, the initial treatment should consist of one of the following:
  - Ampicillin 500 mg four times daily orally.
  - Erythromycin 500 mg four times daily orally or azithromycin 500 mg once a day.
  - Doxycycline 100 g twice a day orally.
- In moderate to severely ill cases, the treatment consists of the following:
  - Ceftriaxone 2 g IV once a day or cefotaxime 1–2 g 8 hourly.
  - Fluoroquinolone (e.g. levofloxacin 750 mg once a day).
  - Amoxycillin–clavulanic acid 1.2 g 8 hourly intravenously.
- Total duration of therapy in an uncomplicated case is 5–7 days.

Vaccine

- Two types:
  - The pneumococcal polysaccharide vaccine (PPV) consists of 23 most common capsular serotypes that cause invasive pneumococcal disease in the developed world. Its effectiveness is hampered by poor responses in elderly people, immunocompromised patients and in children younger than 2 years (precisely those at greatest risk for severe pneumococcal disease).
  - Second vaccine is polysaccharide–protein conjugate pneumococcal vaccine (pneumococcal conjugate vaccine – PCV) that generally targets seven serotypes responsible for most of pneumococcal infections in children. It is approved for use mainly in children younger than 2 years and adults above 50 years. It also induces herd immunity

as it reduces the frequency of invasive pneumococcal disease infection in non-vaccinated siblings and even adult contacts. A 13-valent PCV is also available.

Indications

- Age >65 years
- Patients with risk factors:
  - Congestive heart failure
  - Asthma and COPD
  - Diabetes mellitus
  - Chronic liver disease
  - Alcoholism.
- Splenectomised patients including patients with sickle cell anaemia.
- Persons living in long-term care facilities.
- Immunocompromised persons.

Q. Give a brief account of staphylococcal pneumonia.

- Caused by *Staphylococcus aureus*.
- Common following influenza, in debilitated patients in hospital and in those with cystic fibrosis.
- Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important pathogen in nosocomial pneumonia.
- Recently, community-acquired MRSA (CA-MRSA) infections (skin and soft tissue infections and necrotizing pneumonia) occurring in previously healthy persons have emerged as a serious clinical concern.
- Abscess formation is very common. The abscesses are thin walled, multiple and often bilateral.
- Abscesses may rupture into pleura to produce pneumothorax or pyopneumothorax.
- Chest radiograph shows bronchopneumonia, often bilateral, with multiple thin-walled cyst-like lesions (pneumatoceles).
- Sputum smear shows gram-positive cocci in clumps.

Antibiotic Therapy

- If the infection is not severe, second generation cephalosporins (cefuroxime), amoxycillin–clavulanic acid, fluoroquinolones or macrolides (erythromycin, azithromycin, clarithromycin) are used.
- If the infection is severe, third or fourth generation cephalosporins (cefotaxime, ceftriaxone or cefepime) should be used.
- If methicillin-resistant organisms are suspected as in nosocomial infections or in locations where prevalence of CA-MRSA is significant, vancomycin (1 g IV twice a day) or linezolid (600 mg twice a day) should be given. Linezolid belongs to oxazolidinone group of antibiotics. It is useful in infections caused by gram-positive organisms including MRSA, multiresistant strains of *S. pneumoniae* and vancomycin-resistant *Enterococcus faecium* (VRE).

Q. Give a brief account of Klebsiella pneumonia (Friedlander's pneumonia).

- Caused by *Klebsiella pneumoniae* (Friedlander's bacillus).
- Common in alcoholics and diabetics.
- Severe illness with a high mortality rate.
- Massive consolidation of one or more lobes, the upper lobes being most often involved. Abscess formation and pleural effusion are common.
- The sputum may be viscid, jelly like and blood stained (currant jelly sputum), but may be purulent or rusty.
- Chest radiograph shows an air space pneumonia, usually in one of the upper lobes, with abscess formation and pleural effusion. Bulging interlobar fissure is a characteristic finding.
- Sputum smear shows Gram-negative bacilli. *Klebsiella pneumoniae* can be isolated from the sputum.

Antibiotic Therapy

- Gentamicin, ceftazidime or ciprofloxacin is given for a period of 2–3 weeks. In severe cases, piperacillin + tazobactam or meropenem should be given.

- Extended-spectrum β-lactamases (ESBL) producing organisms have increasingly been reported. In such cases, treatment options include meropenem (or imipenem + cilastin), amikacin and tigecyclin. Polymyxin B can be considered against highly resistant strains.

Q. Discuss the aetiology, clinical features, investigations and treatment of atypical pneumonias.

Q. Give a brief account of legionella pneumonia (Legionnaire's disease).

- Atypical pneumonias are caused by three organisms: *Legionella pneumophila*, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* (now known as *Chlamydophila pneumoniae*).
- Suspect an atypical organism as the cause of pneumonia if patient has three or more of the following:
  - Age <60 years.
  - No underlying co-morbid condition.
  - Paroxysmal cough.
  - No expectoration.
  - Few clinical signs on chest examination.
- If total leucocyte count <10,000/mm^3 is added to the above five parameters, then presence of ≥4 features indicates a strong likelihood of atypical pneumonia.

Legionella Pneumonia or Legionnaire's Disease

- Transmitted in water droplets originating in infected humidifier cooling systems and from stagnant water in cisterns and showerheads. Person-to-person spread has not been reported.
- Clinical features are fever with chills and cough with scanty mucoid sputum. Gastrointestinal symptoms like nausea, abdominal pain and diarrhoea, and mental confusion or delirium are common.
- Among cases of CAP with atypical causes, legionnaires' disease has the most severe clinical course, and illness can become progressively more severe if the infection is not treated appropriately and early. Uncommon features include myocarditis, pericarditis and prosthetic valve endocarditis, as well as glomerulonephritis, pancreatitis and peritonitis.
- Chest radiograph shows parenchymal lesions progressing from patchy to lobar consolidation. Pleural effusion may be seen in more than one-third patients. Complete clearing of infiltrates may take 1–4 months.
- Relative lymphopenia, very high ESR, hyponatraemia, proteinuria and microscopic haematuria are common.
- The organism is not visible on Gram staining. Sputum and bronchoscopic specimens should be sent for culture. Direct fluorescent antibody test on sputum is highly specific but less sensitive than sputum culture.
- Specific diagnosis is often made by a four fold or greater rise in indirect fluorescent antibody in the serum. Another moderately sensitive method is to demonstrate legionella antigen in the urine.
- Another disease caused by *Legionella* is Pontiac fever, which is a self-limiting and flu-like illness.

Mycoplasma Pneumonia

- Caused by *Mycoplasma pneumoniae*, an organism which lacks cell wall.
- It is the pathogen most often associated with atypical pneumonia.
- Onset is insidious, over several days to a week.
- Constitutional symptoms include headache exacerbated by cough, malaise, myalgias and sore throat. Cough is usually dry, paroxysmal and worse at night.
- Clinical course is usually mild and self-limited.
- Pulmonary complications include effusion, empyema, pneumothorax and respiratory distress syndrome.
- Extrapulmonary manifestations include skin manifestations (erythema multiforme, erythema nodosum, maculopapular and vesicular eruptions, and urticaria), neurologic involvement (aseptic meningitis, encephalitis, Guillain–Barre syndrome and transverse myelitis), myocarditis, pericarditis and pancreatitis.
- Production of cold agglutinins can result in haemolytic anaemia.
- Diagnosis:
  - Mild leucocytosis may be present.
  - Four fold rise in antibody titres.
  - Cold agglutinins are non-specific but help in diagnosis.

Chlamydia Pneumonia

- *Chlamydophila pneumoniae* is an obligate intracellular organism.
- Transmission results from contact with respiratory secretions.
- Incubation period is several weeks.
- More likely to occur in older patients with co-morbid diseases than in those who are otherwise healthy.
- Presentation is usually with sore throat, headache, low-grade fever and cough that can persist for months.
- Chest radiographs tend to show less-extensive infiltrates than are seen with other causes of pneumonia.
- Another species of *Chlamydophila* that can cause pneumonia is *C. psittaci*. It generally causes disease in birds. Occasionally, humans can get infected (psittacosis). Doxycycline is the drug of choice.

Antibiotic Therapy of Atypical Pneumonias

- Erythromycin or one of the other macrolides (clarithromycin or azithromycin) is the drug of choice.
- Doxycycline is also an effective drug.
- Fluoroquinolones have excellent activity against all three atypical organisms. In addition, fluoroquinolones have the advantage of once-daily dosing and excellent bioavailability, whether they are given intravenously or orally.
- β-lactams are not effective.

Q. Give a brief account of actinomycosis.

- Caused by *Actinomyces israeli*, an anaerobic organism existing in the mouth as a commensal.
- When local defences are impaired, it can result in disease. Three forms of the disease are recognised:
  - Oral-cervicofacial actinomycosis with soft tissue swelling, abscess and discharging sinuses.
  - Abdominal actinomycosis with discharging sinuses, abdominal mass or abscess.
  - Pulmonary actinomycosis with widespread suppurative pneumonia, empyema (often bilateral) and persistent discharging chest wall sinuses.
- Pus from the sinuses contains "sulphur grains".

Antibiotic Therapy

- Benzylpenicillin 18–24 million units intravenously (in four divided doses) for 4–6 weeks followed by oral penicillin for 6–12 months.

Q. Give a brief description of pneumonias caused by viruses (viral pneumonias).

- Influenza, parainfluenza, measles, varicella (chickenpox) and respiratory syncytial virus are the commonly implicated pathogens.
- Other viral pneumonias include SARS and Middle East Respiratory Syndrome produced by novel *Coronaviruses*.

Clinical Features

- The clinical picture differs from that of bacterial pneumonias in a number of aspects.
- Fever and toxaemia usually precede respiratory symptoms by several days.
- Severe headache, malaise and anorexia are characteristic early features.
- Physical signs in the chest are absent or minimal whereas radiological findings are striking.
- Splenomegaly may be present during the first week.
- Leucocyte count is usually normal and the condition may not respond to penicillins.
- Diagnosis is confirmed by isolation of virus, serological tests and RT-PCR.
- Viral pneumonias are usually self-limiting. Fever subsides in 5–10 days, followed by complete clinical recovery and radiographic resolution.
- Death occurs from complications like widespread extension of pneumonia or viral encephalitis.

Treatment

- Treatment is mainly supportive with oxygenation and cardiopulmonary support.
- Varicella can be treated with intravenous acyclovir or vidarabine.
- Treatment of influenza pneumonia includes use of oseltamivir, zanamivir, amantadine or rimantadine.
- Ribavirin is effective for respiratory syncytial virus infection.

Q. Give a brief account of acute bronchopneumonia.

- It is a type of secondary pneumonia, invariably preceded by bronchial infection. It is particularly common in patients with chronic bronchitis. The lesions are bilateral and patchy, often extensive in the lower lobes.
    - In children, it occurs as a complication of measles or whooping cough.
    - In adults, it occurs as a complication of acute bronchitis or influenza.
    - In elderly or debilitated patients, it is described as "hypostatic pneumonia".
- Viral pneumonias and "atypical" pneumonias may also be present as bronchopneumonia.

Clinical Features

- High fever, severe cough with purulent expectoration, breathlessness, tachycardia, tachypnoea and central cyanosis.
- In early stages, physical signs in the chest are those of acute bronchitis, but later crepitations become more numerous.
- Chest radiograph shows bilateral mottled opacities, predominantly in the lower zones.
- Neutrophil leucocytosis is common.

Antibiotic Therapy

- Ampicillin or cotrimoxazole given orally is effective in mild bronchopneumonia.
- In serious cases, a third-generation cephalosporin along with a macrolide should be used.

Q. Describe eosinophilic pneumonias.

Q. Discuss in brief about pulmonary infiltrates with eosinophilia.

Q. Briefly discuss chronic eosinophilic pneumonia (Carrington's disease).

Q. What is tropical pulmonary eosinophilia? Explain.

- Pulmonary infiltrates with eosinophilia or eosinophilic pneumonias are characterised by eosinophilic pulmonary infiltrates and peripheral eosinophilia.
- Features include:
    - Peripheral blood eosinophilia with abnormal pulmonary imaging studies (chest X-ray and/or CT chest).
    - Eosinophilia in lung parenchyma in transbronchial or open lung biopsies.
    - Increased eosinophils in bronchoalveolar lavage (>10%).

Pulmonary Infiltrates with Eosinophilia—Causes

- Allergic bronchopulmonary aspergillosis (ABPA)
- Drug reactions (e.g. nitrofurantoin, sulphonamides, penicillins, thiazides, isoniazid, para-aminosalicylic acid, imipramine, chlorpropamide, daptomycin)
- Parasitic infestations (e.g. filaria, roundworm, hookworm)
- Loeffler's syndrome
- Acute eosinophilic pneumonia
- Chronic eosinophilic pneumonia (CEP)
- Churg–Strauss syndrome
- Hypereosinophilic syndrome
- Tropical pulmonary eosinophilia

Loeffler's Syndrome

- A benign, acute eosinophilic pneumonia due to migrating larvae of *Ascaris lumbricoides, Ancylostoma duodenale, Necator americanus* and *Strongyloides stercoralis* through lungs.
- Migratory pulmonary infiltrates on imaging with minimal clinical features (an irritating, non-productive cough and burning substernal discomfort). Uncommon features include dyspnoea, wheezing, fever and blood-tinged sputum containing eosinophil-derived Charcot–Leyden crystals.

- Stool examination generally negative at the time of pulmonary symptoms.
- Specific therapy not required.

Acute Eosinophilic Pneumonia

- Acute febrile illness of unknown cause.
- Patient may develop acute respiratory failure.
- Pulmonary infiltrates, severe hypoxia. Occasionally, pleural effusion.
- Lasts for <7 days.
- Peripheral eosinophilia rare at presentation but develops during the course of disease.
    - Bronchoalveolar lavage shows increased eosinophils (>25%).
    - Treatment includes supportive care and steroids.

Chronic Eosinophilic Pneumonia (Carrington's Disease)

- Chronic eosinophilic pneumonia (CEP) is a disease of an unknown cause.
- The hallmark of CEP is eosinophil accumulation in the lungs.
- Female preponderance with a peak incidence in the fifth decade.
- Onset is insidious with weight loss, cough, dyspnea, wheezing and night sweats.
- Airway obstruction may develop during the course of CEP.
- Chest X-ray usually shows bilateral peripheral shadows, which may be migratory.
- Peripheral eosinophilia (>1000/mm^3) is usual.
- BAL reveals eosinophilia (eosinophils >25% of lavage fluid cells).
- Standard treatment is with oral steroids; however, relapses are common when daily steroid dose is reduced below 15 mg. Long-term oral steroids are often required.
- Treatment with inhaled steroids may be of some value.

Hypereosinophilic Syndromes (HES)

- A group of disorders with sustained overproduction of mature eosinophils (hypereosinophilia) with eosinophilic infiltration of organs causing their damage.

Diagnostic Criteria

Hypereosinophilia
- Presence of >1500 eosinophils/mm^3 in blood on two examinations separated in time by at least one month and/or tissue hypereosinophilia

Tissue hypereosinophilia
- Bone marrow showing eosinophils >20% of all nucleated cells, and/or
- Tissue infiltration that is extensive in the opinion of a pathologist, and/or
- Marked deposition of eosinophil granule proteins in tissue (in the absence or presence of major tissue infiltration by eosinophils)

Organ damage
- Eosinophil-mediated organ damage and/or dysfunction, provided other potential causes for damage have been excluded.

Classification

• Primary (or neoplastic) HES	An underlying stem cell, myeloid, or eosinophilic neoplasm (clonal expansion)	
• Secondary (or reactive) HES	Overproduction of eosinophilopoietic cytokines by other cell types (polyclonal). Examples include heavy parasitic infections, certain solid tumours, and T cell lymphoma	
• Idiopathic HES	Underlying cause unknown despite thorough work-up	

Clinical Features and Treatment

- Features of multiple organ involvement (e.g. cardiac involvement—myocarditis, endomyocardial fibrosis, tricuspid valve involvement, pulmonary involvement—dyspnoea, cough, parenchymal infiltrates, pleural effusion; skin involvement—eczema, dermographism, erythroderma, urticaria; CNS involvement—encephalopathy, thromboembolism, peripheral neuropathy, etc.).
- Treatment involves use of corticosteroids and hydroxyurea along with management of organ dysfunction. Some patients may require imatinib.

Tropical Pulmonary Eosinophilia

Definition

- Tropical eosinophilia is a hypersensitivity response to a helminthic parasite, particularly filarial parasite (*Wuchereria* and *Brugia*).
- The syndrome is characterised by pulmonary manifestations and peripheral blood eosinophilia of more than 2000/mm³.

Aetiology

- Tropical eosinophilia is an allergic reaction to helminthic parasites, particularly filarial worms.
- Other parasites implicated are ascaris, toxocara and ankylostoma.

Clinical Features

- Tropical eosinophilia can present in various forms:
  - Asymptomatic form
  - Respiratory form (commonest)
  - Alimentary form
  - A form with constitutional disturbances
  - A form with generalised lymphadenopathy and hepatosplenomegaly.
- The common respiratory form may be either acute or chronic.
  - The acute type presents with high-grade fever, exertional breathlessness and cough with scanty expectoration.
  - The chronic type presents with vague ill health, low-grade fever, exertional dyspnoea and cough with scanty expectoration.
  - Physical signs include bilateral rhonchi and crepitations, particularly basal.

Investigations

- Total leucocyte count is raised.
- Peripheral blood eosinophilia of more than 2000/mm³.
- Raised serum IgE levels (>1,000 units/mL).
- Raised filaria-specific IgG and IgE levels.
- Microfilariae are absent in peripheral smear
- Sputum examination shows clumps of eosinophils and Charcot–Leyden crystals.
- Chest radiograph and CT chest (high-resolution) shows bilateral, diffuse, fine mottling in many patients.
- Pulmonary function tests show restrictive and obstructive ventilatory defects.

Treatment

- Diethylcarbamazine 6 mg/kg/day in divided doses for 3 weeks.
- Long-standing and resistant cases are treated with prednisolone and bronchodilators.

Q. Give a brief account of aspiration pneumonia.

- It occurs due to abnormal entry of fluid, particulate exogenous substances or endogenous secretions into the lower airways. It is of two types: chemical aspiration pneumonia and bacterial aspiration pneumonia.
- Other aspiration syndromes include lung abscess and exogenous lipoid pneumonia.

Predisposing Factors

- Reduced consciousness (including following anaesthesia).
- Dysphagia from neurologic deficits.
- Disorders of the upper gastrointestinal tract including oesophageal disease, surgery involving the upper airways or oesophagus, and gastric reflux.
- Mechanical disruption of the glottic closure or cardiac sphincter due to tracheostomy, endotracheal intubation, bronchoscopy, upper endoscopy and nasogastric feeding.
- Miscellaneous conditions such as protracted vomiting, large volume tube feedings and feeding gastrostomy.

Chemical Aspiration Pneumonia

- It occurs due to the aspiration of substances that are toxic to the lower airways, independent of bacterial infection. It includes chemical pneumonitis associated with the aspiration of gastric acid (Mendelson's syndrome).

Clinical Features

- Abrupt onset of symptoms with low-grade fever and prominent dyspnoea.
- Examination reveals cyanosis and diffuse crepitations.
- Chest radiograph shows infiltrates involving dependent pulmonary segments that usually develop within 2 hours of aspiration.
- Some patients have a fulminant course and die shortly after aspiration, presumably from ARDS. Others have a rapid clinical improvement with clearing of the chest radiograph. Another subset of patients have initial rapid improvement but then develop new expanding infiltrates on chest radiograph that probably represent secondary bacterial infection superimposed on the acid-injured lung.

Treatment

- Tracheal suction to clear fluids and particulate matter.
- Support of respiration including mechanical ventilation, if required.
- Use of corticosteroids is controversial.
- Antibiotics are often given though there is no evidence that bacteria are important in acute events.

Bacterial Aspiration Pneumonia

- The most common form of aspiration pneumonia is caused by bacteria that normally reside in the upper airways or stomach.
- Generally seen in hospitalised patients who have depressed gag reflex, impaired swallowing, or nasogastric or endotracheal tube. Also seen in elderly persons and patients with impaired consciousness due to drug and alcohol ingestion, stroke, etc.

Clinical Features

- The presenting findings in aspiration pneumonia due to bacterial infection are highly variable and depend upon the bacteria involved and status of the host.
- Most cases involve anaerobic bacteria that normally reside in the gingival crevices.
- Most patients present with the usual manifestations of pneumonia including cough, fever, purulent sputum and dyspnoea, but the process evolves over a period of several days or weeks instead of hours.
- Many patients have accompanying weight loss and anaemia caused by the chronic process.
- Oral examination may reveal periodontal disease.

Diagnosis

- The presence of putrid discharge in sputum is regarded as diagnostic of anaerobic infection.
- Chest radiograph shows involvement of dependent pulmonary segments that are favoured in aspiration; the lower lobes when aspiration occurs in upright position; and the apical segments of the lower lobes or posterior segment of the upper lobes when aspiration occurs in recumbent position.

Treatment

- Previously, antibiotic of choice for the treatment of aspiration pneumonia and lung abscess involving anaerobic bacteria was penicillin. However, approximately 25% of cases involve penicillinase-producing anaerobic bacteria.
- Clindamycin (600 mg 8 hourly IV followed by 300 mg 6 hourly orally) is now the preferred drug for anaerobic infections above the diaphragm, including pulmonary infections.
- Alternative regimens that appear effective include amoxycillin–clavulanate or newer fluoroquinolones (levofloxacin and gemifloxacin).
- Do not use metronidazole alone since monotherapy is associated with a failure rate of about 50%.

Q. What is meant by hospital-acquired pneumonia (nosocomial pneumonia)? How will you manage them?

- Pneumonia developing in hospital in a patient who has been admitted for more than 48 hours should be considered as hospital acquired. The infection should not be in the incubation state at the time of admission.
- A subcategory of nosocomial pneumonia is VAP that occurs in patients who have been on ventilatory support for any reason. Pneumonia is categorised as VAP if it occurs after 48 hours of mechanical ventilation. Early-onset VAP occurs within the first 4 days of hospitalisation, whereas late-onset VAP develops 5 or more days after admission. Late-onset pneumonias are usually associated with multidrug-resistant (MDR) organisms.
- The organisms causing hospital-acquired pneumonias are different from those causing CAP.
- The range of organisms causing hospital-acquired pneumonias is very wide, but there is a predominance of Gram-negative bacteria like *Pseudomonas* species, *Escherichia* species, *Klebsiella* species, *Staphylococcus aureus*, *Acinetobacter* species and *Enterobacter* species.

Risk Factors for Nosocomial Pneumonia

- Aspiration of oropharyngeal secretions
- Supine position in hospitalised patients
- Prolonged hospital stay
- Cigarette smoking
- Increasing age
- Uraemia
- Alcoholism
- Prior antibiotic use
- Endotracheal intubation
- Malnutrition
- Neutropenia
- Stress ulcer prophylaxis using histamine blockers and proton pump inhibitors (PPI)

- Nosocomial pneumonia is clinically diagnosed in patients who have been hospitalised for at least 48 hours and subsequently develop a new or progressive infiltrate on chest imaging, accompanied by at least two of the three systemic signs: fever, leucocytosis, and purulent sputum.
- Patients with hospital-acquired pneumonia should have blood cultures and vigorous attempts must be made to obtain respiratory secretions for identification of the organism and determining its sensitivity to antibiotics.
- Empiric therapy generally consists of a third generation cephalosporin along with an aminoglycoside (gentamicin or amikacin).
- If multiantibiotic resistance is a problem in the hospital, then pneumonia due to Gram-positive organisms should be treated with vancomycin or teicoplanin or linezolid. For Gram-negative pneumonia, a β-lactam active against *Pseudomonas* (ceftazidime, cefoperazone, cefepime, piperacillin + tazobactam or meropenem) or a fluoroquinolone (ciprofloxacin or levofloxacin) + an aminoglycoside should be used.
- Another approach is "de-escalation therapy" in which combination of antibiotics active against both Gram-positive and Gram-negative organisms are initiated keeping in mind the locally available data on resistance pattern. The antibiotics are scaled down once the results of cultures are available.

Prevention of Ventilator-Associated Pneumonia

- Rigorous hand washing by caregivers
- Semirecumbent positioning of the patient to prevent aspiration
- Adequate nutritional support
- Avoidance of gastric distention
- Early removal of endotracheal and nasogastric tubes
- Continuous subglottic suctioning
- Use of sucralfate (for stress-ulcer prophylaxis)
- Avoidance of prophylactic antibiotic

Q. How do you classify mycobacteria? Give an account of diseases produced by them.

Q. Describe mycobacteria other than tuberculosis (MOTT).

Q. Write a brief note on nontuberculous mycobacteria (NTM).

- Mycobacteria are divided into three groups:
  - *Mycobacterium tuberculosis* complex (*M. tuberculosis*, *M. bovis* and *M. africanum*).
  - *Mycobacterium leprae*.
  - Atypical mycobacteria or nontuberculous mycobacteria (NTM) or mycobacteria other than tuberculosis (MOTT).
- MOTT or NTM are ubiquitous in the environment. Therefore, their isolation from a site that is not normally sterile (e.g. sputum, skin or urine) does not constitute proof of disease. Evidence of human-to-human transmission is lacking.
- Classical method for the isolation of mycobacteria is their culture on a solid medium (like LJ medium). However, this may take as long as 2–3 months.
- Culture in liquid broth using the radiometric BACTEC system shortens the time needed to culture mycobacteria.
- Molecular probes are now used for the rapid identification of some important species.
- Traditionally, based on growth rates and pigment production in the culture, NTM have been classified into four groups (Runyon classification): slow-growing NTM and fast-growing NTM (Group IV). Slow-growing NTM are further subclassified into three categories based on pigment production in the culture.
  - Group I—Photochromogens (P) that are pigment producers in the presence of light.
  - Group II—Scotochromogens (S) that are pigment producers in the absence of light.
  - Group III— Nonchromogens (N) that do not produce any pigment.
- Patients with NTM pulmonary disease often have predisposing structural lung disease, i.e. chronic obstructive pulmonary disease, cystic fibrosis, bronchiectasis, pneumoconiosis, prior tuberculosis or chronic aspiration.

Diseases Caused by Various NTM and their Treatment

| Agent | Disseminated disease | Localised disease | | | Treatment |
		Lungs	Lymph nodes	Skin	
• *M. avium intracellulare* complex (N)	Yes; typical in AIDS with CD4 cells <50/μL (fever, night sweat, diarrhoea, abdominal pain, weight loss with or without hepatosplenomegaly; blood and bone marrow cultures may be positive)	Cavities in cystic fibrosis and COAD	Yes (accounts for 80% cases of NTM-associated lymphadenitis	Rare	Rifabutin, clarithromycin and ethambutol; add streptomycin in severe cases. For lymphadenitis, complete excision of involved lymph node, if feasible

| Agent | Disseminated disease | Localised disease | | | Treatment |
		Lungs	Lymph nodes	Skin	
• M. kansasii (P)	Rare	Yes	Rare	Rare	Rifampicin, INH, ethambutol, streptomycin
• M. marinum (P)	Rare	–	Rare	Yes	Cotrimoxazole, ethambutol, rifampicin, clarithromycin
• M. ulcerans (N)	Rare	–	–	Yes (Buruli's ulcer)	Debridement
• M. xenopi (S)	Rare	Rare	–	–	Same as for M. avium
• M. szulgai (S)	Rare	Rare	–	Yes	Rifampicin, INH, ethambutol
• M. scrofula-ceum (S)	Rare	Rare	Yes	Rare	Same as for M. avium
• M. fortuitum (group IV)	Rare	Rare	Rare	Yes	Imipenem, Amikacin, ciprofloxacin, sulphonamides, clofazimine
• M. chelonae (group IV)	Rare		–	Yes	Debridement, clarithromycin, imipenem, clofazimine, amikacin, linezolid

Q. Discuss the pathogenesis, pathology, clinical manifestations and diagnosis of primary pulmonary tuberculosis.

Q. Write in brief about primary complex of Ranke and Ghon's complex.

Pathogenesis and Pathology

- First infection of the lung with the tubercle bacillus is known as primary pulmonary tuberculosis.
- Mycobacteria are carried in airborne particles (droplet nuclei) of 1–5 microns in diameter. Transmission occurs when a person inhales droplet nuclei containing *M. tuberculosis* and the droplet nuclei traverse the mouth or nasal passages, upper respiratory tract and bronchi to reach the alveoli of the lungs.
- From this primary site of infection, bacilli are carried to the lymph nodes via lymphatics and the hilar nodes enlarge. This parenchymal lesion (Ghon's lesion) with its enlarged regional (hilar) lymph nodes and interconnecting lymphangitis is known as the primary complex of Ranke (Ghon's complex).
- The parenchymal lesion is subpleural and is usually located in lower part of the upper lobe, upper part of the lower lobe or the middle lobe.
- Bacilli in alveoli also invade and replicate within alveolar macrophages that interact with T lymphocytes, resulting in differentiation of macrophages into epithelioid histiocytes. Epithelioid histiocytes and lymphocytes aggregate into small clusters resulting in granulomas. In the granuloma, CD4+ T lymphocytes secrete cytokines, such as interferon-γ, which activate macrophages to destroy the bacteria with which they are infected. CD8+ T lymphocytes (cytotoxic T cell) can also directly kill infected cells.

- The above-mentioned immunological reaction occurs after about 3–8 weeks of infection (by the time of tuberculin conversion), when the classical pathological features of tuberculosis may be found in varying proportions. This is a granulomatous lesion containing epithelioid cells derived from macrophages, Langhans' giant cells with multiple nuclei also derived from macrophages, lymphocytes and varying degrees of fibrosis. Later, a peculiar cheesy form of necrosis occurs in the centre, known as caseation. The caseous tissue may later become calcified. But if the lesion progresses, the caseous tissue may become liquefied to form purulent material. This material may be discharged into a bronchus resulting in cavitation of the lesion. Cavitation, however, is regarded as one of the manifestations of post-primary pulmonary tuberculosis.
- The pathological changes in the lymph nodes are similar to that of the parenchymal lesion.

Clinical Manifestations

- Primary infection usually occurs in childhood. A history of contact with a case of active tuberculosis is present in many cases.

Symptoms

- Vast majority are asymptomatic.
- A minority may experience a brief flu-like febrile illness, which lasts no more than 7–14 days. It occurs at the time of tuberculin conversion.
- If the infection is severe or the host resistance is low, child may appear to be vaguely unwell with reduced appetite, fretfulness and failure to gain weight.
- Slight dry cough is occasionally present. Wheeze may be rarely present.

Physical Signs

- In vast majority, there are no abnormal physical signs.
- When the lesion is severe or extensive, signs of general debility may be present. Child is thin, pale and fretful with less glossy hair and less elastic skin.
- Usually there are no abnormal physical signs in the chest. Sometimes, there may be a few crepitations over a large lung component of the primary complex. More extensive physical signs in the chest result from complications.
- Erythema nodosum may accompany primary pulmonary tuberculosis. These are bluish-red, raised, tender, cutaneous lesions on the shins and less commonly on the thighs. In some patients, it is associated with fever and polyarthralgia. Tuberculin reaction is strongly positive in this group. Erythema nodosum is also seen in other conditions like sarcoidosis, streptococcal infections and drug reactions.
- Symptoms and signs may result from progression of primary complex or complications of primary complex (refer "fate of primary complex").

Fate of the Primary Complex

- In great majority, the primary focus heals completely with or without calcification. The mechanisms through which the immune system controls the bacilli are not well defined but it is generally believed that the cell-mediated immunity (both CD8+ and CD4+ T cells) plays a critical role.
- In some cases, the primary focus is walled off by collagenous tissue, the tubercle bacilli cease to divide and the disease becomes dormant. However, these dormant lesions can re-activate later giving rise to active post-primary pulmonary tuberculosis.
- In a few individuals, primary lesion in the lung may be actively progressive from the beginning (progressive pulmonary tuberculosis or progressive primary pulmonary tuberculosis).
- In a few cases, healing, particularly in lymph nodes, is incomplete and viable tubercle bacilli may enter the bloodstream. As a result, haematogenous dissemination occurs resulting in tuberculous lesions elsewhere. The haematogenous forms can be of two types:
  - The acute form, which is more likely to occur in infants or young children, results in miliary tuberculosis or tuberculous meningitis.
  - The chronic form where tuberculous lesions develop in the lungs, bones, joints and kidneys. These lesions may develop months or even years after primary infection.

- In some cases, the infection may be carried by lymphatics from mediastinal lymph nodes to pleura or pericardium resulting in tuberculous pleurisy with effusion or tuberculous pericarditis with effusion.
- Bronchial complications resulting from primary complex are the following:
  - Enlarged mediastinal lymph nodes can compress a bronchus resulting in pulmonary collapse. Compression of middle lobe bronchus is especially common, leading to collapse-consolidation and bronchiectatic changes. This may be present later as the "middle lobe syndrome".
  - Tuberculous lymph node may ulcerate through the bronchial wall and discharge caseous material into the lumen. This results in bronchial spread to the related lobe or segment.
  - Rarely, the bronchus is so compressed as to result in a valve action with air trapping. This leads to obstructive emphysema.
  - Calcification in a primary focus or lymph node may later be extruded into a bronchus as a "broncholith", presenting as haemoptysis.

Diagnosis

- History of contact with a case of active tuberculosis.
- Tuberculin test is very valuable in children. A positive test in a previously non-immunised child strongly indicates the disease. A negative test makes the diagnosis very unlikely.
- Chest radiograph can visualise the primary complex as a peripheral parenchymal lesion and an enlarged hilar lymph node.
  - In children, glandular component (enlarged hilar lymph node) of the complex is more obvious than the pulmonary component.
  - In adults, pulmonary component (peripheral parenchymal lesion) of the complex is more obvious than the glandular component.
- Bacteriological examination:
  - Sputum examination is preferable, but it is seldom available. Alternatively, three laryngeal swabs or fasting gastric washings can be examined.
  - Isolation of the tubercle bacilli by direct smear examination or culture confirms the diagnosis.

Q. Discuss the pathogenesis, pathology, clinical manifestations, complications and diagnosis of post-primary pulmonary tuberculosis.

Pathogenesis

- Post-primary pulmonary tuberculosis may arise in any one of the four ways:
  1. Direct progression of a primary lesion.
  2. Re-activation of a dormant primary lesion.
  3. Haematogenous spread to the lungs.
  4. Exogenous superinfection (re-infection).
- Post-primary pulmonary tuberculosis presents mainly as parenchymal disease with only minimal lymph node enlargement. The characteristic pathological feature is the tuberculous cavity which is formed when caseated and liquefied centre of a tuberculous pulmonary lesion is discharged into a bronchus.
- The common sites of involvement are apical and posterior segments of the upper lobe or apical segment of the lower lobe. This predilection may be due to good ventilation and decreased blood and lymphatic supply of these regions in the erect posture.

Conditions that Favour Re-activation/Re-infection of Tuberculosis

- Malnutrition	- Haemophilia
- Diabetes	- Chronic renal failure
- Immunosuppressive treatment (including steroids)	- Silicosis
- HIV infection	- Malignancies

Pathology

Histological Types of Lesions

- In the development of an individual lesion, there is an initial pre-exudate phase that is followed by an exudative phase. In most cases, exudative lesion proceeds to caseation, characterised by development of a cheesy substance.
- Around the edge of the caseation develop the so-called "productive lesions". Here the macrophages transform themselves into epithelioid cells and giant cells (Langerhans' giant cells). Aggregation of epithelioid cells and giant cells into clumps form the classical "tubercles". Lymphocytes are also seen in such lesions. However, there are very few bacilli in such lesions.
- If these lesions regress, fibroblasts appear on the scene leading to deposition of fibrin (fibrosis) at the site of lesion. Caseous material may be reabsorbed or may become walled off by fibrous tissue and get calcified.
- If the lesion proves progressive, the caseous material liquefies and discharges into a bronchus so that a cavity gets formed. The formation of cavity affords a highly favourable breeding ground for the bacilli. The wall of the cavity is usually lined by softened caseous material in which the bacilli thrive. The thickness of the wall varies. In untreated cases, the cavity wall is thick, the lining caseous layer inside is thicker and there may be an outer fibrous layer and superficial to it is a layer of alveolar atelectasis. In properly treated cases, the caseous elements gradually disappear and ultimately a thin-walled epithelialised cavity may be left over. At times, a check-valve mechanism results from the involvement of the bronchial mucous membrane. This allows air to get into a cavity during inspiration, but prevents its escape during expiration. This may result in a large thin-walled cavity. At times, necrotic material inside the bronchus may completely block the lumen, leading to reabsorption of air within the cavity and its closure.
- Secondary lesions may be seen around the main lesion or cavity or in other parts of both lungs. These may result from bronchial spill over or haematogenous spread.

Macroscopic Appearances

- If the lesions are limited, upper lobes are commonly involved. A whole lobe may be involved (tuberculous pneumonia).
- Large caseous areas and cavities are characteristic features of post-primary pulmonary tuberculosis. Cavities may be single or multiple, sometimes multilocular, of varying size with varying thickness of the walls. Sometimes, a pulmonary vessel may be seen running across a cavity.
- In chronic disease, there is gross fibrosis and distortion of lung architecture. In addition, there may be calcification and bronchiectasis.

Clinical Features

Symptoms

- Many patients are symptom-free, and tuberculosis may be detected on routine radiography.
- A characteristic feature of tuberculosis is the gradual onset of symptoms over weeks or months.
- Any patient who has had cough for more than 2 weeks or fever for >2 weeks with or without associated weight loss or night sweats should be investigated for pulmonary tuberculosis.

General Symptoms

- Loss of weight and loss of appetite.
- Fever, especially evening rise of temperature.
- Night sweats.
- Tiredness, malaise.
- Mental symptoms.
- Amenorrhoea.

Respiratory Symptoms

- Cough is the most consistent symptom.
- Sputum, which may be mucoid, purulent or blood stained.
- Haemoptysis is a classical symptom.
- Pain in the chest resulting from pleurisy, intercostal myalgia or cough fracture.
- Breathlessness is a feature of advanced and extensive disease.

- Localised wheeze resulting from local ulceration and narrowing of a major bronchus.
- Recurrent cold is at times a presenting symptom.
- Pneumonia (with acute presentation) that turns out to be tuberculous is another mode of presentation.

Physical Signs

- Pallor and cachexia in advanced cases.
- Fever, tachycardia and tachypnoea.
- Finger clubbing is unusual, but it may be present in chronic disease with purulent sputum.

Physical Signs in the Chest

- Often there are no abnormal signs.
- The most common sign is fine crepitations in the upper part (apices) of one or both lungs. These are heard particularly on taking a deep breath after coughing (post-tussive crepitations). Later, there may be dullness to percussion or even bronchial breathing in the upper part. At times, there is a localised wheeze due to local tuberculous bronchitis or pressure by a lymph node on a bronchus. In chronic tuberculosis with fibrosis, evidence of volume loss and mediastinal shift may be present.
- Classical physical signs of consolidation, cavitation, collapse, fibrosis, bronchiectasis, pleural effusion or pneumothorax may be present.

Complications of Pulmonary Tuberculosis

- Haemoptysis	- Persistence of cavities even after treatment
- Pneumothorax	- Infection of cavities by Aspergillus
- Secondary infection of cavity	- Scar carcinoma
- Pleural effusion	- Spread of tuberculosis to other organs
- Empyema	- Respiratory failure and right heart failure
- Pulmonary fibrosis	- Amyloidosis
- Bronchiectasis	- Anaemia

Investigations

Blood Examination

- Moderate anaemia.
- White cell count is usually normal or below normal.
- ESR is usually raised.
- Hyponatraemia and hypokalaemia may be present in severe disease.
- Impaired liver function tests are occasionally seen.

Radiological Examination of Chest

- A normal chest radiograph for practical purposes excludes tuberculosis. The radiological features of tuberculosis are given ahead in the chapter.
- CT chest may be useful in evaluating parenchymal lesions and lymph nodes.
- ^{18}F-FDG PET scans and ^{11}C-choline PET scans may be done in selected patients.

Sputum Examination

- Microscopic examination of sputum smear remains the most important investigation. WHO recommends that two sputum samples should be examined for screening of tuberculosis cases in places where a well functioning external quality-assurance system exists, where the workload is very high and human resources are scarce. Presence of at least one acid fast bacillus in at least one sputum sample in such samples indicates sputum-positive pulmonary tuberculosis.
  1. A first spot specimen when the patient presents himself.
  2. An early morning specimen consisting of all sputum raised in the first 1–2 hours.
- If quality assurance system is not available, then three specimens of sputum should be examined.

1. A first spot specimen when the patient presents himself.
2. An early morning specimen consisting of all sputum raised in the first 1–2 hours.
3. A second spot specimen when the patient returns with an early morning specimen.
   • A smear-positive pulmonary tuberculosis case is defined as one with:
     a. two or more initial sputum smear examinations positive for acid fast bacillus, or
     b. one sputum smear examination positive for acid fast bacillus plus radiographic abnormalities consistent with active pulmonary tuberculosis as determined by a clinician, or
     c. one sputum smear positive for AFB plus sputum culture-positive for *M. tuberculosis*.
• Sputum culture for tubercle bacillus may be done, but results become available only in 4–8 weeks. Drug resistance tests should be done in selected cases. In all settings with an HIV prevalence of >1% in pregnant women or ≥5% in patients with tuberculosis, sputum culture should be performed in patients who are sputum smear-negative.

Laryngeal Swabs

• While taking a swab, the patient coughs and the swab catches some mucus. This is sent for culture.

Gastric Aspiration (Gastric Lavage or Gastric Washings)

• May be used in children as sputum is difficult to get from them. Early morning fasting (at least 4 hour in children and 3 hours in infants) gastric washings can show tubercle bacilli. For this, a sterile nasogastric tube is introduced into the stomach and 20 mL of sterile normal saline is injected. After 1 minute aspirate out as much as possible. The aspirate should be examined by smear and culture.

Bronchoalveolar Lavage

• Bronchoalveolar lavage fluid gives more positive results, but it is reserved for selected cases.

Tuberculin Test

• Tuberculin testing as a tool for diagnosis is much less valuable. This is partly because the test may be negative due to malnutrition or other diseases even when the patient has active tuberculosis. On the other hand, many people without active tuberculosis have positive tests.
• A strongly positive test is a point in favour of tuberculosis, but a negative test does not exclude tuberculosis.

T-Cell Interferon-γ Release Assays (IGRAs)

• T-cell based interferon-γ (IFN-γ) assays are in vitro tests of cellular immunity. These assays measure cell-mediated immune response by quantifying IFN-γ released by T cells in response to stimulation by *Mycobacterium tuberculosis* antigens.
• Currently two ex-vivo assays are available: the ELISpot (T-SPOT™.TB) that directly counts the number of IFN-γ secreting T-cells and the whole-blood ELISA (QuantiFERON™-TB Gold In-Tube) that measures the concentration of IFN-γ secretion.
• Both the tests incorporate antigens that are more specific to *M. tuberculosis*. These specific antigens include early secretory antigenic target-6 (ESAT-6) and culture filtrate protein-10 (CFP-10). These antigens are not shared by any BCG strains or most non tuberculous mycobacteria (except *M. kansasii*, *M. marinum* and *M. szulgai*). Therefore, in comparison with the tuberculin skin test, T-cell responses to these antigens are not confounded by prior BCG vaccination and hence a more specific marker of TB infection.
• Compared to tuberculin skin test, IFN-γ-based tests do not show boosting effect on repeated tests. However, this test requires high cost and trained personnel. Further, a positive IFN-γ test does not indicate active infection as it is also positive in latent tuberculosis.
• WHO recommended against the use of IGRAs for diagnosis of active or latent TB in resource-limited setting.

Other Methods of Diagnosis

• In MGIT (Mycobacteria growth indicator tube) method, growth is detected by a non-radioactive detection system using fluorochromes for detection and drug screening.
• BACTEC radiometric growth detection: In this method, ^{14}C-labelled palmitic acid is incorporated in a liquid culture medium. Growth of bacilli is detected by liberation of $^{14}CO_2$, produced as a result of metabolism of palmitic acid by viable mycobacteria. The growth can be detected in 4–8 days.

- Microscopic-observation drug-susceptibility (MODS) assay which detects *M. tuberculosis* bacilli on the basis of cording formation, as well as isoniazid and rifampicin resistance.
- Molecular methods: Nucleic acid amplification tests (NAAT) are rapid tests that can detect small amounts of genetic material (DNA or RNA target sequences) from the micro-organism, and are based on repetitive amplication of target sequences. If the target organism is not present in the sample no amplification will occur. A variety of amplification methods may be used, including amplification of the target nucleic acid, such as the polymerase chain reaction (PCR) or amplification of a nucleic acid probe, such as a ligase chain reaction. These methods can detect mycobacteria in cultured material or in clinical sample directly.
  - Line-probe assays and microfluidic PCR device (GeneXpert®) allow both rapid detection of TB and also drugs resistance patterns. GeneXpert may give results within 2 hours and detects resistance to rifampicin. Line probe assays detect resistance to both rifampicin and isoniazid.
- Mycobacterial-specific phages (reporter phages) to detect luciferase gene. Can be used to detect drug-resistant isolates.

Q. Enumerate the causes of haemoptysis in pulmonary tuberculosis.

Haemoptysis from a Pulmonary Cavity

- Walls of the vessels traversing a cavity undergo atrophic changes due to inflammatory and necrotic degeneration.
- Over a period of time these vessels develop aneurysmal dilatation. These aneurysms (Rasmussen's aneurysm) rupture resulting in haemoptysis.
- Occasionally, intense allergic response to antigens of tubercle bacilli damage the walls of the vessels in and around the cavities, which results in haemoptysis.

Haemoptysis from Endobronchial Tuberculosis

- Endobronchial tuberculomas (tuberculous granulomas) are surrounded by vessels with small aneurysmal dilatation. Rupture of these aneurysms results in haemoptysis.
- Alternatively, as a result of secondary infection, part of the granuloma may slough out resulting in haemoptysis.

Haemoptysis as a Sequela of Pulmonary Tuberculosis

- A cavity may persist despite complete epithelialisation following therapy. Such cavities are termed as "open-healed cavities". The aneurysmal dilations would also persist in these open-healed cavities. These aneurysms can rupture resulting in haemoptysis.
- Bronchiectasis of the upper lobe is a common sequela of pulmonary tuberculosis ("post-tuberculous bronchiectasis"). This presents as bronchiectasis sicca or dry bronchiectasis, characterised by repeated attacks of haemoptysis without sputum production.
- Calcification in a primary focus or lymph node may later be extruded into a bronchus as a "broncholith", which causes haemoptysis. Haemoptysis results from the broncholith eroding through blood vessels.
- Well treated and "healed" tuberculous cavities sometimes remain open and can be infected by the fungus Aspergillus fumigatus. This results in a fungal ball (aspergilloma), which can present as severe haemoptysis.

Q. Give a brief account of sputum smear examination for mycobacteria.

Q. What are the common causes of false positive and false negative results of sputum examination?

Collection of Sputum

- Patient should be taught what constitutes "sputum", and how to produce proper bronchial sputum from the "depths of the chest". Saliva and nasopharyngeal secretions are unsuitable for examination.
- If the patient discharges acid-fast bacilli in his sputum, these are more likely to be found in a specimen produced early morning than in one produced later during the day. Hence, the ideal sputum specimen is the one which is produced in early morning, before breakfast and before taking any medicaments. For convenience, three samples as stated above are collected on 2 days. However, at present, WHO recommends two samples for diagnosis when external quality-assurance system is in place. Another recent move is to examine two samples on the same day ("same-day" diagnosis).

- The patient should rinse his mouth with pure water and clean his teeth (without using toothpaste or disinfectant) before coughing out the sputum specimen. If repeated attempts of coughing have failed, aerosol induction (should be done in a separate, well-ventilated room), gastric aspiration and bronchoscopy may be required.

Storage and Transport of Sputum and Storage of Stained Specimens

- The collected sputum should not be exposed to direct sunlight or excessive heat.
- While storing stained specimens, immersion oil on the slide should be removed with xylol.
- Fluorochrome will lose fluorescence with storage.

Preparation of Smears

- If the quantity of sputum is sufficient, it is better to concentrate the specimen before preparing the smears. A solution of 4% sodium hydroxide is added to the sputum (2 parts with 1 part of sputum) and incubated for 1 hour. Then it is concentrated by centrifugation. The supernatant is removed by pipette and the deposit is used for preparation of smears.
- If concentration is not done, select the suitable sputum particles for smear preparation. Tubercle bacilli are most likely to be found in little blobs ("lentils") of greenish-grey or yellowish matter of a thick, creamy consistency. Such blobs usually consist of dead caseous tissue eliminated from a cavity in the lung. These blobs have to be carefully separated from the rest of the sputum and transferred to a slide.
- The specimen is transferred to a new glass slide (with no scratches) with a wire loop of internal diameter 3 mm (WHO standard). The wire loop transfers roughly 0.01 mL of sputum. This sputum is spread over an area of 200 mm^2 (10 mm × 20 mm). The smear should be fixed by passing it over a Bunsen flame taking care not to overheat it.

Wire loop and slide used for the preparation of sputum smears

Wire loop with internal diameter 3 mm
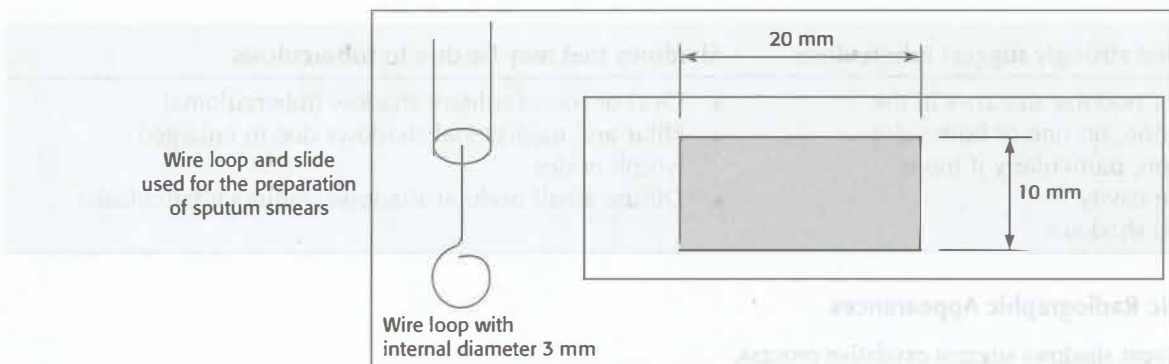
Staining Techniques

- Two methods of staining for tubercle bacilli are in common use:

Ziehl–Neelsen Method

- The fixed smears are kept on staining racks. Smears are covered with suitably cut filter papers. Carbol fuchsin is poured over the filter paper and gently heated till the smear steams. The smears are then washed under tap water. Next, 25% sulphuric acid is added on the smear and the smear is allowed to decolourise for 2½ minutes. The smear is then washed twice in water and again decolourised with 95% alcohol for 2 minutes. It is again washed in water and counterstained with 0.1% methylene blue for 10 seconds and dried. The dried smear is examined under oil immersion.

Fluorochrome Staining

- The fixed smear is covered with 0.3% auramine phenol for 15 minutes, then washed with water and decolourised twice with 0.5% acid-alcohol for 2 minutes. The smear is then treated with 0.1% potassium permanganate solution for 30 seconds. The specimen is then washed and dried for examination under fluorescent microscope. It is more sensitive than conventional Z–N stain and microscopy. Presently, it is recommended that conventional fluorescence microscopy be replaced by LED (light-emitting-diode) microscopy while assessing auramine staining.

- The field observed through the fluorescent microscope is much larger than that observed through the oil immersion lens, hence a larger area can be covered in shorter duration.
- However, fluorescent microscope requires high cost and maintenance, advanced technical skill for operation and continuous electric supply with steady voltage.

False-Positive Results

- Acid-fast particles other than tubercle bacilli can give false positive results. These include some food particles, precipitates, other micro-organisms, inorganic materials and artifacts. These particles when treated with Ziehl–Neelsen are allowed to decolourise.
- Besides mycobacteria, some other organisms may show some acid fastness (but not to 25% sulphuric acid) and include *Nocardia*, *Rhodococcus*, *Isospora* and *Cryptosporidium*.

False-Negative Results

- Inadequate sputum collection.
- Inadequate storage of sputum specimens and stained smears.
- Failure to select suitable sputum particles for smear preparation.
- Inadequate preparation of smears or staining slides.
- Inadequate examination of the smear.

Q. List down the radiological features of pulmonary tuberculosis.

- A normal chest radiograph for practical purposes excludes pulmonary tuberculosis.

Shadows that strongly suggest tuberculosis	Shadows that may be due to tuberculosis
• Patchy or nodular shadows in the upper zone, on one or both sides • Cavitation, particularly if more than one cavity • Calcified shadows	• Oval or round solitary shadow (tuberculoma) • Hilar and mediastinal shadows due to enlarged lymph nodes • Diffuse small nodular shadows (miliary tuberculosis)

Characteristic Radiographic Appearances

- Soft confluent shadows suggest exudative process.
- Linear shadows, especially if they produce distortion of fissures, trachea, mediastinum or diaphragm, suggest fibrosis.
- Tuberculomas—large solid-looking areas which contain caseation and productive lesions and measure 0.5–4.0 cm in diameter. Satellite nodules around the tuberculoma may be present in as many as 80% of cases. Because of active glucose metabolism caused by active granulomatous inflammation, tuberculomas may accumulate ^{18}F-FDG and produce hot-spots in PET scans (like malignant lesions).
- Very dense white shadows suggest calcification.
- Elongated translucent areas in the upper zones suggest bronchiectasis.
- CT is useful in demonstrating cavities, calcification, tuberculomas and lymph nodes. Enlarged nodes typically show central low attenuation, which represents caseous necrosis, and peripheral rim enhancement, which represents the vascular rim of the granulomatous inflammatory tissue. Another important finding on CT chest is "tree-in-bud" sign—branching linear and nodular opacities; these reflect endobronchial spread and are due to the presence of caseous necrosis and granulomatous inflammation filling and surrounding terminal and respiratory bronchioles and alveolar ducts.
- Pleural effusion, empyema, aspergilloma, etc. may be seen on radiograph. These should be considered as complications of pulmonary tuberculosis.
- Cavitation can be made out only if the liquefied materials are coughed out and air gets into the cavity. Cavities may be single or multiple, small or large. The wall of the cavity may be thin or thick, regular or irregular.
  - In early stages, the cavity wall is thick and irregular. In the chronic phase, the wall is thin and regular.
  - During chemotherapy the cavity wall becomes thinner and smoother.

- Thin-walled bullous cavities may be seen in treated cases.
- Distended thin-walled cavity may result from a check-valve mechanism operating in the draining bronchus.
- A cavity may become "blocked". The draining bronchus may be obstructed and instead of the cavity collapsing, it may become filled with purulent or caseous material ("blocked cavity").

Q. Write a short note on tuberculin testing.

Q. What is Mantoux test?

- First infection with the tubercle bacillus leads to the development of sensitisation to the protein "tuberculin". When tuberculin (purified protein derivative or PPD) is injected into the skin of an infected person, a delayed local reaction develops in 24–48 hours. This is mainly due to previously sensitised CD4+ lymphocytes.

Tuberculins

- There are two common tuberculins in present use:
  1. PPD-S has been adopted as the international standard for PPD of mammalian tuberculin.
  2. PPD-RT23 is widely used in epidemiological studies throughout the world. RT stands for Research Tuberculin. Tween 80 is a detergent added to tuberculin to prevent its adsorption on glass or plastic surface. Its is most commonly used in India.
- PPD is a mixture of over 200 *M. tuberculosis* proteins.

Mantoux Test

- It is ideal to begin the test with 5 IU PPD-S or 1 or 2 IU PPD-RT23.

Method

- Choose an area of skin at the junction of the mid and upper thirds of flexure surface of the left forearm. Clean the area with soap and water and allow it to dry. Using a tuberculin syringe and an intradermal needle, inject 0.1 mL of the tuberculin solution strictly intradermally. It should produce a papule in the skin 5–6 mm in diameter.

Reading and Interpreting the Result

- The test is read after 48–72 hours. If a reaction has taken place, there will be an area of erythema (redness) and an area of induration (thickening) of the skin. Measure the diameter of induration across the transverse axis of the arm. The amount of erythema (redness) present is not important.
- A positive reaction is an area of induration of the skin with a diameter of 10 mm or more. This is one point in favour of the diagnosis. But remember that many normal people have a positive test and so also after previous BCG vaccination. Most infants immunised with BCG at birth have a negative tuberculin test by 1–2 years. In infants immunised after 1 year, the tuberculin reaction often remains positive for some years. It may also be positive in NTM infections. However, a strongly positive test is particularly valuable in children, especially very young children.
- If the diameter is below 10 mm, the test is negative. But a negative test does not exclude tuberculosis. A patient with active tuberculosis may have a suppressed tuberculin test (false negative) due to a number of factors—e.g. malnutrition, viral infections, HIV infection, measles, chickenpox, glandular fever, cancer, severe bacterial infections (including tuberculosis), corticosteroids and similar drugs.

Q. How do you make an assessment of activity of tuberculosis?

- A positive sputum, especially if repeated, certainly indicates activity.
- Presence of symptoms like cough, tiredness or weight loss, is suggestive of activity.
- Detection of crepitations on auscultation, if persistent, is in favour of activity.
- There are certain radiological appearances that are suggestive of activity:
  - The presence of a cavity always indicates activity unless proved otherwise.
  - Soft shadows, even if very small, are suggestive of activity.

- If shadows are extensive, activity is very probable.
- Progression of shadows in serial X-rays suggests activity.
- A raised ESR may indicate an activity.
- A strongly positive tuberculin test is quite compatible with an active lesion, but a negative or weakly positive test is not very likely in the presence of activity (see "false negative" above).

Q. Describe latent tuberculosis infection.

- Latent tuberculosis infection is a condition in which a person is infected with *M. tuberculosis*, but does not currently have active tuberculosis disease. During latent infection, the host immune system is able to contain the bacilli in a state of non-replicating persistence.
- An estimated 2 billion persons worldwide have latent infection and are at risk for reactivation.

Groups of People at High Risk of Latent Tuberculosis Infection

- Employees of long-term care facilities, hospitals and medical laboratories
- Persons who have close contact with someone known or suspected to have active tuberculosis
- Residents and employees of congregate living facilities, including prisons and jails, nursing homes, hospitals and homeless shelters
- Some medically underserved, low-income populations

- Patients with latent tuberculosis are at risk of progressing to active tuberculosis. About 5–10% is the lifetime risk of progression.

Groups at Increased Risk of Progression

- Children younger than five years
- Persons with HIV infection
- Persons infected with *Mycobacterium tuberculosis* within the past two years
- Injectable drug users
- Persons with a history of untreated or inadequately treated tuberculosis
- Silicosis
- Persons with immunocompromising conditions:
  - Long-term use of corticosteroids or other immunosuppressants (including anti-TNF-α)
  - Chronic renal failure
  - Diabetes mellitus
  - Malignancy

Screening for Latent Tuberculosis

- Tuberculin test.
- T-cell IGRAs.

Prophylaxis (to Prevent Development of Active Tuberculosis)

- Persons deemed to have latent tuberculosis and who are at increased risk for progression to active TB should be considered candidates for preventive therapy.
- Please see tuberculosis prophylaxis.

Q. What do you understand by the terms "bactericidal action" and "sterilising action" in relation to antituberculous drugs?

- Bactericidal action is defined as the ability of antituberculous drugs to kill large numbers of actively metabolising bacilli rapidly.
  - Most of the antituberculous drugs with the exception of the bacteriostatic drugs such as thiacetazone and PAS have bactericidal action. Isoniazid is the most potent bactericidal drug.
  - Ethambutol is bacteriostatic at low doses and bactericidal at high doses.
- Sterilising action is defined as the capacity of antituberculous drugs to kill special populations of slowly or intermittently metabolising semi-dormant bacilli, the so-called "persisters". Rifampicin and pyrazinamide are the main sterilising drugs.

Q. What are antituberculous drugs and what are their dosages in adults?

Q. Discuss modes of action of first-line drugs.

| Drug | Daily dosage | | Intermittent dosage | |
	Weight	Dose	Weight	Dose
First-line drugs				
• Isoniazid (H)	–	5 mg/kg	–	10 mg/kg/three times weekly
		300 mg (maximum)	–	–
• Rifampicin (R)	<50 kg	450 mg	–	10 mg/kg/three times weekly
	≥50 kg	600 mg	–	–
• Streptomycin (S)	<50 kg	15 mg/kg	<50 kg	15 mg/kg
	≥50 kg	1.0 g	≥50 kg	1.0 g
• Pyrazinamide (Z)	<50 kg	1.5 g (25 mg/kg)	<50 kg	35 mg/kg
	≥50 kg	2.0 g	≥50 kg	2.5 g three times weekly
• Ethambutol (E)	–	25 mg/kg for 2 months followed by 15 mg/kg	–	30 mg/kg three times weekly
Second-line drugs				

Fluoroquinolones

| Drug | Daily dosage | | Intermittent dosage | |
	Weight	Dose	Weight	Dose
• Ofloxacin (Ofx)	–	400 mg BID		
• Levofloxacin (Lfx)	–	750 mg–1 g OD	–	–
• Moxifloxacin	–	400 mg OD		

Oral Bacteriostatic Drugs

| Drug | Daily dosage | | Intermittent dosage | |
	Weight	Dose	Weight	Dose
• Ethionamide (Eto)	<50 kg	750 mg (in two divided doses)		
	≥50 kg	1.0 g (in two divided doses)	–	–
• Prothionamide (Pto)	<50 kg	750 mg (in two divided doses)	–	–
	<50 kg	1.0 g (in two divided doses)		

• Cycloserine (Cs)	<50 kg	750 mg (in two divided doses)	–	
	≥50 kg	1.0 g (in two divided doses)		
• Terizidone (Trd)	<50 kg	750 mg (in two divided doses)	–	
	≥50 kg	1.0 g (in two divided doses)		
• Para-aminosalicylate Sodium (PAS)	–	10–15 g	–	–

Parenteral Agents

• Kanamycin (Km)	<50 kg	750 mg	–	–
	≥50 kg	1.0 g	–	–
• Capreomycin (Cm)	<50 kg	750 mg	–	–
	≥50 kg	1.0 g	–	–
• Amikacin (Amk)	<50 kg	750 mg	–	–
	≥50 kg	1.0 g	–	–

Mode of Action of first-Line Antituberculous Drugs

- In a tuberculous lesion, particularly a cavity, mycobacteria exist in several foci. These foci and the drugs acting on them are:
  - Extracellular, in alkaline medium—Streptomycin.
  - Rapidly metabolising mycobacteria (generally in a cavity)—Rifampicin.
  - Less actively multiplying bacilli in acidic and closed lesions—Isoniazid.
  - Dormant bacilli (which cause a relapse)—Pyrazinamide.

Other Drugs

- β-lactams (imipenem, amoxycillin and clavulanic acid), linezolid, clofazimine, clarithromycin, dapsone and metronidazole have been used occasionally for multidrug resistant TB, but their roles are not well established.
- A new drug approved for MDR tuberculosis is bedaquiline.

Q. Describe rifampicin-related antitubercular agents.

Rifabutin

- It is active against *M. tuberculosis*.
- It is also active against some rifampicin-resistant strains of *M. tuberculosis* and is more active against *M. avium intracellulare* complex as compared to rifampicin.
- It is recommended in the treatment of tuberculosis in HIV-infected patients who are on protease inhibitors.
- Dose is 150 mg/day. Patients taking rifabutin also have discoloured (orange) body secretions.
- Adverse effects include GI distress, rash, myalgias and insomnia. Less common side effects are flu-like syndrome, anterior uveitis, leucopenia, skin discolouration and hepatitis.

Rifapentine

- It is lipophilic and has a longer duration of action.
- Strains resistant to rifampicin are also resistance to this drug.
- Dose is 600 mg once or twice a week.
- It may be used in the treatment of pulmonary tuberculosis in place of rifampicin.
- Side effects are similar to those of rifampicin.

Q. What are the side effects of the commonly used antituberculous drugs?

Drug	Adverse reactions
Isoniazid	Uncommon—Hepatitis, cutaneous hypersensitivity, peripheral neuropathy (preventable and treatable with pyridoxine) Rare—Giddiness, convulsions, optic neuritis, mental symptoms, haemolytic anaemia, aplastic anaemia, agranulocytosis, lupoid reactions, arthralgia, gynaecomastia
Rifampicin	Uncommon—Hepatitis, cutaneous reactions, gastrointestinal reactions, thrombocytopenic purpura, febrile reactions (flu-like syndrome; more common with intermittent therapy) Rare—Shortness of breath, shock, haemolytic anaemia, acute renal failure
Streptomycin and other aminoglycosides	Common—Cutaneous hypersensitivity, giddiness, numbness, tinnitus Uncommon—Vertigo, ataxia, deafness, hypokalaemia Rare—Renal damage, aplastic anaemia, agranulocytosis
Pyrazinamide	Common—Anorexia, nausea, flushing Uncommon—Hepatitis (dose related), vomiting, arthralgia, cutaneous hypersensitivity Rare—Sideroblastic anaemia, photosensitivity
Ethambutol	Uncommon—Retrobulbar neuritis (dose related), arthralgia Rare—Hepatitis, cutaneous hypersensitivity, peripheral neuropathy
Ethionamide	Common—Anorexia, vomiting Uncommon—Serious neurologic reactions, hepatitis Rare—Hypothyroidism
Cycloserine*	Common—Headache, somnolence Uncommon—Psychosis, seizures, peripheral neuropathy, suicidal ideation
Quinolones	Common—GI intolerance, skin rashes Uncommon—Phototoxicity (with sparfloxacin), dizziness, headache, insomnia Rare—Confusion, seizures, interstitial nephritis, vasculitis, acute renal failure, prolonged QT interval, hyperglycaemia, tendon rupture
PAS	Common—Gastrointestinal reactions Uncommon—Hepatitis, cutaneous hypersensitivity, hypokalaemia Rare—Acute renal failure, haemolytic anaemia, thrombocytopenia, hypothyroidism

*Terizidone may have less CNS side effects compared to cycloserine.

Q. Discuss regimen of antituberculous chemotherapy.

Potent 6-month regimens

- When there is a low rate of initial drug resistance (recommended standard 6-month regimen):
  - 2HRZ/4HR

- When there is a high level of initial drug resistance:
  - 2EHRZ/4HR
  - 2SHRZ/4HR

- When fully supervised intermittent chemotherapy can be organised:
  - $2HRZ/4H_3R_3$
  - $2E_3H_3R_3Z_3/4H_3R_3$
  - $2S_3H_3R_3Z_3/4H_3R_3$

Note

1. The number used as prefix indicates number of months of treatment. The number used as subscript indicates frequency per week.
2. Even though evidence showed equivalent efficacy of daily intensive-phase dosing followed by two times weekly continuation phase, twice weekly dosing is not recommended on operational grounds, since missing one dose means the patient receives only half the regimen.

Q. What is short-course chemotherapy? What are the advantages of short-course chemotherapy?

- Short-course chemotherapy is now widely accepted as the treatment of choice for tuberculosis. Short-course chemotherapy includes 6-month regimen (refer "regimens of chemotherapy").
- Short-course regimens are divided into two phases: an initial or bactericidal phase and a continuation or sterilizing phase.
- During the initial phase, majority of mycobacteria are killed, symptoms resolve and the patient becomes non-infectious.
- During continuation phase, the semi-dormant "persistors" are eliminated.

Advantages of Short-Course Chemotherapy

- It is easy to take and produces fewer upsets in the patients.
- The patient feels better more quickly.
- The sputum becomes negative more quickly, 85% negative at 2 months compared with only 50% in older 12-month regimens.
- The relapse rate is low.
- If relapse does occur, the tubercle bacilli remain sensitive and the same treatment can be given again.

Q. What is the "fall and rise" phenomenon?

- The "fall and rise" phenomenon is observed in inadequately treated patients.
- Sputum smear is positive at the commencement of therapy. Thereafter, the sputum bacillary content declines, and it becomes negative on smear microscopy and positive only on culture—the "fall". Still later, the sputum bacillary content increases and the sputum smear becomes positive again—the "rise".
- What actually occurs in "fall and rise" phenomenon is the "fall" of drug-sensitive bacilli and the "rise" of drug-resistant mutants of the strain. This is because the drug-resistant bacilli rapidly outgrow rest of the drug-sensitive bacilli. This results in the drug-resistant mutants completely replacing the drug-sensitive bacilli, and finally the strain becoming fully resistant.

Q. How can the progress of treatment be monitored and the treatment result assessed?

- The main method of monitoring the progress of treatment and assessing the final result is bacteriological examination. Other less useful methods include radiological assessment, ESR and body weight changes.

Bacteriological Assessment

- Bacteriological assessment is done by examining sputum by smear and culture. Serial sputum smear examinations alone would clearly indicate the progress and ultimate result. Culture examinations are merely confirmatory and are indicated only in selected cases.
- Sputum smear examination—see DOTS below:
- A treatment failure may be indicated by various patterns:
  - Persistence of sputum bacilli (no response).
  - An initial decline followed by a steady rise in sputum positivity ("fall and rise" phenomenon).
  - An initial decline and sputum negativity, followed much later by sputum positivity (relapse).

Radiological Assessment

- Serial chest radiographs can be used to assess progress and determine final result. Grossly, if serial radiographs show improvement, this may be considered as a favourable response.
- It is important to note that radiological assessment can be misleading many times. Patients with radiological improvement may still discharge tubercle bacilli. On the other hand, bacteriologically quiescent cases may show no radiological improvement or even worsening.

Erythrocyte Sedimentation Rate

- Erythrocyte sedimentation rate (ESR) is not a very satisfactory method of assessing the progress or activity of disease in patients on chemotherapy. However, a fall in ESR may be considered as a favourable response.

Body Weight Changes

- Body weight changes are also not very reliable. However, a gain in body weight may be considered as a favourable response.

Q. Discuss the directly observed treatment, short course (DOTS).

Q. What is stop TB strategy?

- Directly observed treatment, short-course or DOTS means administering potent antimycobacterial regimens in an intermittent manner to a patient with tuberculosis under direct supervision.
- Despite short-course therapy, tuberculosis remains the leading infectious cause of death in India, killing close to 370,000 people a year (i.e. roughly 1000 every day). India has far more cases of tuberculosis than any other country in the world—about 2 million new cases each year of which 800,000 are infectious. Daily therapy is excellent; however, it is expensive and not suitable for supervised therapy and hence compliance rate is low and relapse rate is high.
- DOTS is the backbone of Revised National TB Control Programme (RNTCP) in India.
- The basic objectives of RNTCP are:
  - To treat successfully 85% of detected smear-positive cases.
  - To detect 70% of all such cases.
- DOTS is a five point programme that can ensure effective TB control:
  - Political and administrative support.
  - Diagnosis by sputum microscopy in patients attending health facilities.
  - Good drugs for short-course chemotherapy.
  - Directly observed treatment that should be accessible, acceptable and accountable.
  - Systematic monitoring and accountability.

Progress Under RNTCP

- The Revised National Tuberculosis Control Programme (RNTCP) based on the DOTS strategy began as a pilot in 1993 and gradually expanded to cover a population of 20 million by mid 1998. Rapid RNTCP expansion began in late 1998. By the end of 2000, 30% of the country's population was covered, and by the end of 2002, 50% of the country's population was covered under the RNTCP. By the end of 2003, 778 million population was covered, and the coverage reached to 997 million at the end of year 2004. By December 2005, around 97% (about 1080 million) of the population had been covered, and the entire country has been covered under DOTS by 24th March 2006.

Implementation of DOTS

- Patients with cough for 2 weeks or more are encouraged to attend the nearest health care facility for sputum examination over a 2-day period (one spot on the day of attending the health facility, second next day morning sample collected at home, and the third spot sputum when the patient comes to deposit the second sample). However, at present, only two sputum samples are advised in countries with active external quality-assurance system, high workload and limited human resources, and if one is positive, it indicates active tuberculosis.
- If one or two of the smears are positive for acid-fast bacilli, antituberculosis treatment is initiated. If all two (three if external quality-assurance system is lacking) smears are negative, 1–2 weeks of broad-spectrum antibiotics are prescribed. If broad-spectrum antibiotics are used, fluoroquinolones should be avoided. A trial of broad-spectrum antibiotics is not recommended to be used as a diagnostic aid for smear-negative pulmonary TB in persons living with HIV.
- If symptoms persist after the administration of broad-spectrum antibiotics, a chest radiograph is obtained, usually at a larger health centre, and the patient is evaluated.
- For DOTS, the patients with tuberculosis are categorised into three categories (previously four categories) and treatment is given as per the recommendations.

Important Definitions

- New case: A patient who has never had antituberculous treatment or had for <1 month.
- Relapse: A patient previously treated for tuberculosis and declared cured and is now diagnosed bacteriologically positive tuberculous case.
- Treatment failure: A patient who has not responded to antituberculous treatment.
- Treatment defaulter: A patient who had treatment for tuberculosis for at least 1 month, then interrupted it for at least 2 months and now has bacteriologically positive tuberculosis.
- Chronic case: A patient who continues to be bacteriologically positive despite completing standard antituberculous treatment.
- Multidrug resistant tuberculosis is defined as resistance to isoniazid and rifampicin whether there is resistance to other drugs or not.

Categories of Tuberculosis

- In 2009, WHO gave a new classification for tuberculosis patients:
  - New patients:
    - New patients have never had treatment for tuberculosis, or have taken anti-tubercular drugs for <1 month. New patients may have positive or negative bacteriology and may have disease at any anatomical site.
    - New patients with pulmonary TB may receive a daily intensive phase followed by daily continuation phase [2HRZE/4HR] or daily intensive therapy followed by a three times weekly continuation phase [2HRZE/4(HR)$_3$], provided that each dose is directly observed OR $2H_3R_3Z_3E_3$ followed by $4H_3R_3$ provided that every dose is directly observed and the patient is NOT HIV positive or living in an HIV-prevalent setting)—except for tuberculosis of meninges, bones and joints, and lymph nodes, where duration may be 9–12 months.
    - In populations with known or suspected high levels of isoniazid resistance (e.g. India), new TB patients may receive HRE as therapy in the continuation phase as an acceptable alternative to HR
- Previously treated patients:
  - These are patients who have received 1 month or more of anti-tubercular drugs in the past. A culture and drug sensitivity test should be performed at the time of starting treatment. Further subdivided into:
    - Relapsed group (cured initially with completed treatment)—may start with retreatment with first-line drugs but depends on local resistance pattern in such patients.

- Default group (a patient whose treatment was interrupted for 2 consecutive months or more)—may start with retreatment with first-line drugs but depends on local resistance pattern in such patients
- Failure group (a patient whose sputum smear or culture is positive at 5 months or later during treatment. Also included in this definition are patients found to harbour a multidrug-resistant strain at any point of time during the treatment)—should receive empirical treatment for MDR tuberculosis while waiting for sputum culture and drug sensitivity.
- For relapsed and default group, re-treatment regimen is 2HRZES/1HRZE/5HRE or $2H_3R_3Z_3E_3S_3/1H_3R_3Z_3E_3/5H_3R_3E_3$—drugs are modified after drug-sensitivity results become available
- Others:
  - All cases that do not fit the above definitions, such as patients for whom it is not known whether they have been previously treated; who were previously treated but with unknown outcome of that previous treatment; and/or who have returned to treatment with smear-negative pulmonary tuberculosis.

Dosages of Drugs in Intermittent Therapy

- Rifampicin—10 mg/kg; 450 mg if weight <60 kg; patients weighing >60 kg are given an additional 150 mg)
- Isoniazid—10 mg/kg (maximum 900 mg)
- Pyrazinamide—35 mg/kg
- Streptomycin—15 mg/kg with a maximum of 1000 mg (500–750 mg if the patient is above the age of 50 years)
- Ethambutol—30 mg/kg

Operational Aspects of DOTS

- Specimens for culture and drug susceptibility testing should be obtained from all previously treated TB patients at or before the start of treatment. Drug susceptibility test should be performed for at least isoniazid and rifampicin. Rapid molecular methods (e.g. GeneXpert) for detection of drug resistance should be used if available.
- For smear-positive pulmonary TB patients (both new and re-treatment groups), sputum smear microscopy may be performed at completion of the intensive phase of treatment.
- In patients treated with the regimen containing rifampicin throughout treatment, if a positive sputum smear is found at completion of the intensive phase, the extension of the intensive phase is not recommended.
  - In new patients, if the specimen obtained at the end of the intensive phase (month two) is smear-positive, sputum smear microscopy should be obtained at the end of the third month.
  - In new patients, if the specimen obtained at the end of third month is smear-positive, sputum culture and drug susceptibility testing should be performed.
  - In previously treated patients, if the specimen obtained at the end of the intensive phase (month three) is smear-positive, sputum culture and drug susceptibility testing should be performed.
- Sputum specimens for smear microscopy should be obtained at the end of months 5 and 6 for all new pulmonary TB patients who were smear-positive at the start of treatment. Patients whose sputum smears are positive at month 5 or 6 (or who are found to harbour MDR-TB strains at any time) should be re-registered as having failed treatment.
- Every dose of medication in the initial phase is directly observed, either by a health-worker or by a community member who is not a family member. In the 4 to 5 month continuation phase when the bacterial load is far lower, at least the first of each of the thrice-weekly doses is directly observed.
- Medications for both phases of treatment are kept in an individual box containing the entire course of treatment for a single patient. For the intensive phase, each blister pack contains 1 day's medication. For the continuation phase, each blister pack contains 1 week's supply of medication.
- TB patients with known positive HIV status and all TB patients living in HIV-prevalent settings should receive daily TB treatment at least during the intensive phase. For the continuation phase, the optimal dosing frequency is also daily for these patients. However, if a daily continuation phase is not possible for these patients, three times weekly dosing during the continuation phase is an acceptable alternative. Antiretroviral treatment (ART) should be initiated for all HIV-positive patients with active TB disease irrespective of CD4 cell count. Treatment for TB should be started first, followed by ART as soon as possible but within the first 8 weeks of starting TB treatment.

Stop TB Strategy

- The vision of Stop TB Strategy is to free the world of tuberculosis.
- Its targets are:
  - Detect at least 70% of new sputum smear-positive TB cases and cure at least 85% of these cases by 2005.
  - Reduce prevalence of and death due to TB by 50% relative to 1990 by 2015.
  - Eliminate TB as a public health problem (<1 case per million population per year) by 2050.
- The new Stop TB Strategy by WHO in 2006 has the following components:
  - Pursue quality DOTS expansion and enhancement by improving the case finding and cure through an effective patient-centred approach to reach all patients, especially the poor.
  - Addressing TB/HIV.
  - Addressing MDR-TB by DOTS-plus (providing drugs for MDR tuberculosis).
  - Health system strengthening by collaborating with other health programmes and general services.
  - Involvement of all care providers including NGOs and private doctors.
  - Engaging people with TB and affected communities.
  - Enabling/promoting research for developing new drugs, diagnostics and vaccines.

Q. What is DOTS-plus strategy?

- Applicable to areas where prevalence of MDR-tuberculosis is high. Outcome of the standard short-course regimen remains uncertain. Unacceptable failure occurs and resistance to additional agents may be induced. DOTS-plus provides additional services in such areas to provide high cure rate and reduce transmission.
- DOTS-plus modifies all the elements of the DOTS strategy:
  - Treatment may need to be individualised rather than standardised.
  - Laboratory services may need to provide facilities for on-site culture and drug-susceptibility testing.
  - Reliable supplies of a wide range of expensive second-line agents.
  - Operational studies required to determine the indications of modified treatment.
  - Financial and technical support from international organisations needed in addition to that obtained from local governments.

Q. What are the forms of drug resistances encountered during antituberculous chemotherapy?

Q. What are the common causes of drug resistance?

Primary Drug Resistance and Initial Drug Resistance

- Primary drug resistance occurs in patients who have either not received any antituberculous chemotherapy before or received it for less than 1 month. It is caused by infection—i.e. by the transmission of drug-resistant organisms from another patient with secondary resistance due to inadequate chemotherapy.
- When it is impossible to obtain a reliable history of previous chemotherapy from a new, drug-resistant patient, it is better to use the term initial drug resistance. This term would cover true primary as well as undisclosed acquired resistance.

Secondary or Acquired Drug Resistance

- Resistance to one or more drugs, often due to incorrect chemotherapy, is called secondary or acquired resistance.

Natural Drug Resistance

- Strains that have never been exposed to any antibacterial drug are termed "wild strains". A naturally drug-resistant strain is a wild strain resistant to a particular drug without ever coming in contact with it. Thus, neither the patient with naturally resistant bacilli nor his source of infection has had chemotherapy in the past.

Multiple Drug Resistance or Multidrug Resistant (MDR) Strains

- Multidrug resistant tuberculosis is defined as resistance to isoniazid and rifampicin whether there is resistance to other drugs or not. It is therefore incorrect, by this definition, to classify a patient with a multidrug resistant disease if he has an infection with a bacterium susceptible to rifampicin but resistant to many other drugs.

Extensive Drug Resistance (XDR)

- XDR tuberculosis is defined as resistance to isoniazid and rifampicin along with any fluoroquinolone and at least one of the three injectable second-line drugs (capreomycin, kanamycin and amikacin).

Causes of Drug Resistance

• Factors related to previous antituberculous treatment:
   • Inadequate treatment regimen
   • Inadequate supervision of therapy
   • Use of poor quality drugs
   • Poor absorption of drugs
   • Inadequate compliance
   • Development of adverse drug reactions
   • Inadequate duration of treatment
	• Infection due to organisms with primary resistance
	 • Lack of good laboratory facilities to monitor drug susceptibility
	 • Genetic factors

Q. What are various methods for performing drug susceptibility tests for *M. tuberculosis*?

- Lowenstein-Jensen LJ culture for drug sensitivity testing takes about 6–8 weeks time.
- Radiometric methods (BACTEC radiometric method) give results within 10 days of inoculation.
- Mycobacteria growth indicator tube (MGIT) system is a rapid, non-radioactive method for detection and susceptibility testing of *M. tuberculosis*. The MGIT system relies on an oxygen-sensitive fluorescent compound contained in a silicone plug at the bottom of the tube which contains the medium to detect mycobacterial growth. The medium is inoculated with a sample containing mycobacteria and with subsequent growth, mycobacteria utilise the oxygen and the compound fluoresces.
- Nitrate reduction assays are based on the capacity of *M. tuberculosis* to reduce nitrate to nitrite, yielding a visually detected red colour after the Griess reaction. It is performed in the LJ medium. However, some strains of *M. tuberculosis* are nitrate-reductase negative.
- Ligase chain reaction (LCR) involves the use of an enzyme DNA ligase, which functions to link two strands of DNA.
- Luciferase reporter assay is a system for rapid determination of drug resistance. Luciferase is an enzyme identified as the light producing system of fireflies. The luciferase gene is placed into a mycobacteriophage. Once this mycobacteriophage attaches to *M. tuberculosis*, the phage DNA is injected into it and the viral genes are expressed. If *M. tuberculosis* is infected with luciferase reporter phage and these organisms are placed in contact with antituberculous drugs, susceptibility can be tested by correlating the generation of light. It can detect resistant strains within 48 hours.
- PCR-based sequencing to detect mutations responsible for drug-resistance.
- Line-probe assays and GeneXpert to detect drug-resistant (particularly rifampicin resistant) bacilli.

Q. How will you manage a patient with multidrug resistant (MDR) tuberculosis?

- For managing MDR tuberculosis, drugs are categorised into five groups:

Group 1: Most potent and best tolerated (rifampicin, isoniazid, pyrazinamide, ethambutol)
Group 2: Injectable drugs (streptomycin, amikacin, kanamycin, capreomycin)
Group 3: Fluoroquinolones (levofloxacin, moxifloxacin)
Group 4: Oral bacteriostatic agents (ethionamide/prothionamide, cycloserine/terizidone, PAS)
Group 5: Others (clofazimine, linezolid, amoxicillin/clavulanate, imipenem/cilastatin, clarithromycin)

Principles for Managing a Patient with MDR Tuberculosis

- Treatment should be in a specialised centre with standard laboratory facilities
- An appropriate regimen for individual patient needs experience and skill
- The regimen should contain at least four drugs likely to be effective. Selection is based on potency of available drugs, resistance pattern and previous history of treatment. Any first-line oral agent to which the isolate is sensitive should be used. One injectable, one fluoroquinolone and as many second-line bacterostatic agents as needed should be used to make up the four drug regimen in the initial phase of treatment
- For regimens with fewer than four effective drugs, consider adding two group 5 drugs.
- A new drug for MDR tuberculosis is bedaquiline which is a mycobacterial ATP synthase inhibitor.
- Never add a single drug to a failing regimen
- Be careful about cross-resistance. It has been reported between streptomycin and kanamycin or amikacin (capreomycin can be used), between rifampicin and rifapentine (70% of strains will also be resistant to rifabutin), and among various derivatives of fluoroquinolones. Cross-resistance has also been reported between ethionamide and isoniazid
- If possible, give all the drugs in a single daily dose (except PAS)
- Avoid intermittent therapy
- Therapy should be under direct observation preferably for 3–4 months or until sputum conversion
- Surgical treatment should be considered as an adjunct to chemotherapy, wherever applicable as results of chemotherapy are very unpredictable
- In MDR-TB treatment, the intensive phase is defined by the duration of treatment with the injectable agent. The injectable agent should be continued for a minimum of 6 months, and for at least 4 months after the patient first becomes and remains smear- or culture-negative.
- Treatment should be continued for a minimum of 18 months after culture conversion. Extension of therapy to 24 months may be indicated in chronic cases with extensive pulmonary damage.

Q. What are the indications of corticosteroids in the management of tuberculosis?

- Corticosteroids should always be given only in conjunction with antituberculous chemotherapy and never without ATT. They act by reducing the severity both of the local inflammatory reaction and of the associated systemic disturbances.

Indications

- Severe allergic reactions (hypersensitivity) to antituberculous drugs.
- Fulminating, life-threatening pulmonary tuberculosis (keeps the patient alive until the antituberculous drugs begin to act).
- Tuberculous pericardial effusion (reduces outpouring of fluid, reduces adhesions and reduces development of constrictive pericarditis).
- Tuberculosis of the eye, the larynx and ureteric obstruction in renal tuberculosis (reduces fibrosis and scar tissue formation).
- Tuberculous meningitis (reduces adhesions).
- Tuberculous adrenalitis with Addison's disease (replacement of corticosteroids).

Dosage

- In mild conditions, prednisolone is given 10 mg twice daily for 4–6 weeks, followed by a gradual tapering of 5 mg each week.
- In seriously ill patients, particularly tuberculous meningitis, the initial dose should be 60–80 mg daily, tapering gradually as above.

Q. What is extrapulmonary tuberculosis?

- The term extrapulmonary tuberculosis (EPTB) indicates isolated occurrence of tuberculosis at body sites other than the lung. Tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extrapulmonary TB.
- However, when an extrapulmonary focus is evident in a patient with pulmonary tuberculosis, such patients are categorised as pulmonary tuberculosis.
- EPTB constitutes about 15–20% of all cases of TB in immunocompetent patients.
- In HIV-positive patients, EPTB accounts for >50% of all cases of TB.
- TB lymphadenitis is seen in nearly 35% of extrapulmonary TB cases. Cervical lymph nodes are the most common site of involvement and can occur with or without involvement of other lymphoid tissue. Cervical lymphadenitis is also referred to as scrofula. Antituberculous drugs are highly effective in treating lymph node tuberculosis. When lymph nodes are fluctuant, antigravity aspiration should be done.
- Scrofuloderma is a mycobacterial infection of the skin caused by direct extension of tuberculosis into the skin from underlying structures or by contact exposure to tuberculosis.

Pleural	Pleural effusion
Gastrointestinal	Ulcerations of the tongue, intestinal tuberculosis, tuberculous peritonitis
Pericardium	Pericardial effusion and tamponade, constrictive pericarditis
Genitourinary	Renal tuberculosis, salpingitis, tubal abscess, epididymal tuberculosis
Nervous system	Tuberculous meningitis, tuberculous arteritis, cerebral tuberculoma
Lymph nodes	Tuberculous lymphadenopathy (including mediastinal), non-healing sinuses
Skeletal system	Tuberculous osteomyelitis, cold abscess, vertebral tuberculosis, pyarthrosis
Miscellaneous	Addison's disease (tuberculous adrenalitis), skin tuberculosis, phlyctenular keratoconjunctivitis, choroiditis, iritis

Q. Discuss the pathogenesis, types, clinical features, diagnosis and management of miliary tuberculosis in adults.

Q. Write in brief on cryptic miliary tuberculosis.

Q. Describe non-reactive miliary tuberculosis and disseminated non-reactive tuberculosis. Discuss their pathogenesis.

- Classified as pulmonary tuberculosis because there are lesions in the lungs.
- Results from widespread lymphohaematogenous dissemination of tubercle bacilli from a pulmonary or extrapulmonary focus.
- Most commonly involves liver, spleen, bone marrow, lungs and meninges.
- The tubercle bacilli may enter the bloodstream in various ways:
  - Spread to bloodstream from a recent primary infection. This may occur by way of lymph nodes and lymphatics or by a tuberculous lesion with erosion of a blood vessel.
  - Re-activation of an old tuberculous lesion with erosion of a blood vessel.
  - Spread into the bloodstream after a surgical operation on an organ containing a tuberculous lesion.

Types

- Clinically, the patients may be divided into three different types:
  1. Classical (acute) miliary tuberculosis.
  2. Cryptic (obscure) miliary tuberculosis.
  3. Non-reactive miliary tuberculosis.

Classical (Acute) Miliary Tuberculosis

- Can occur at any age, but children and young adults are more affected.
- Onset may be sudden or gradual. An insidious onset of fever, malaise and weight loss over weeks is the usual presentation.
- Systemic disturbances rapidly become profound, with high-grade fever, drenching night sweats and progressive pallor.
- Cough and breathlessness are occasionally present, but there may be no abnormal physical signs in the lungs. Widespread crepitations may be heard late in the disease.
- Hepatosplenomegaly may occur.
- Choroidal tubercles on ophthalmoscopy make the diagnosis certain. They are rare in the elderly.
- Tuberculous meningitis is a common complication. It manifests as neck stiffness and other signs of meningeal irritation.
- ARDS may complicate miliary tuberculosis.
- Without treatment death occurs within days or weeks.
- Chest radiograph may show the characteristic "miliary" mottling (size of millet seeds). Other causes of military shadows on chest radiograph include histoplasmosis, Mycoplasma pneumonia, sarcoidosis, bronchoalveolar carcinoma, lymphangitis carcinomatosis, haemosiderosis (e.g. in long-standing rheumatic heart disease) and occupational lung diseases.
- Total leucocyte count is usually normal or low.
- Tuberculin test may be negative.

Cryptic (Obscure) Miliary Tuberculosis

- Usually occurs in the elderly.
- Often presents as lassitude, weight loss and general debility.
- Prolonged low-grade pyrexia is a common presenting manifestation.
- Anaemia is common and hepatosplenomegaly may occur. Chest is usually normal and choroidal tubercles are rare.
- Without treatment, patient slowly gets worse over months and eventually dies.
- Chest radiograph is usually normal. Miliary mottling may appear after weeks or months. The tuberculin test is usually negative.

Non-Reactive Miliary or Disseminated Tuberculosis

- This condition is rare usually occurring in elderly with disease re-activation.
- It is an acute malignant form of tuberculous septicaemia, resulting in "necrotic" lesions in various organs (no granuloma formation) containing massive number of bacilli.
- The patient is extremely ill and the diagnosis is often missed. If so, the patient dies rapidly.
- The chest radiograph may or may not show miliary mottling, and the tuberculin test is negative.
- Haematological abnormalities are very common. These include anaemia (often aplastic), pancytopenia (especially leucopenia or agranulocytosis) or leukaemoid reaction.

Diagnosis

- Miliary tuberculosis should be suspected in any patient with prolonged fever, miliary mottling on radiograph and choroidal tubercles on fundoscopy.
- Chest radiograph may be virtually diagnostic if it shows the characteristic miliary shadows ("miliary mottling"). These are diffuse small shadows of 1–2 mm diameter. They are evenly distributed throughout both lung fields. Upper zones are always involved. The early lesions may be difficult to visualise. They are better visualised by one of the following methods:
  - Take an overpenetrated (dark) radiograph and shine a bright light behind the outer rib spaces.
  - Lateral chest film.
  - Underpenetrated anteroposterior radiograph.
  - High-resolution CT of chest.
- Positron emission tomography CT (PET-CT) using radiopharmaceutical [18]F labelled 2-deoxy-D-glucose (FDG) may show "hot" spots in areas of active tuberculosis. It can determine the activity of lesions, guide biopsy from active sites and detect occult distant foci,
- Sputum smear is usually negative but bronchoalveolar lavage and bronchial biopsy are most likely to be positive.
- Bacteriological confirmation should be sought by culture of sputum, urine or bone marrow.
- Various haematological abnormalities may be seen, including anaemia, leucopenia, neutrophilic leucocytosis and leukaemoid reaction.
- DIC can develop in a minority of patients.

- Elevation of alkaline phosphatase and other liver enzymes may occur in severe hepatic involvement.
- Hyponatraemia occurs in about 50% cases.
- Bone marrow biopsy may show miliary tubercles or tubercle bacilli on histology. Part of the specimen should be sent for culture for tubercle bacilli.
- Liver biopsy may show miliary tubercles on histology.
- Tuberculin test is only of limited value in the diagnosis of miliary tuberculosis.

Management

- Proved cases of acute and cryptic miliary tuberculosis should be treated with standard antituberculous chemotherapy. If the patient is desperately ill, prednisolone is given along with chemotherapy. This helps to reduce life-threatening toxicity and gives antituberculous drugs time to act.
- If the diagnosis is not proved inspite of strong clinical suspicion (e.g. cryptic miliary tuberculosis), give a therapeutic trial of antituberculous chemotherapy.

Q. Discuss the pathogenesis, clinical features, investigations and management of tuberculous pleural effusion.

- Classically, tuberculous pleural effusion occurs in younger individuals in the absence of pulmonary tuberculosis. However, in one-third of cases, simultaneous pulmonary tuberculosis is present.

Pathogenesis

- Tuberculous pleural effusion results when the pleura is seeded with *M. tuberculosis*. The pleural seeding may occur via lymphatics, blood stream or by direct extension. There may be rupture of subpleural caseous focus into the pleural cavity. This results in the development of delayed hypersensitivity reaction to tuberculous protein (produced by CD4+ cells). It causes increased permeability of pleural capillaries. There may also be some lymphatic block by fibrosis. Since pleural effusion develops as a result of hypersensitivity reaction, mycobacterial cultures of the pleural fluid from most patients with tuberculous pleural effusions are negative.
- Left untreated, the pleura may become very thick and fibrotic ("pleural fibrosis"), and pleural adhesions develop. This later results in a restrictive ventilatory dysfunction. Early treatment will prevent or reduce these sequelae.

Clinical Features

- Classically, in an adolescent or young adult, the illness usually begins as an acute illness with dry cough, fever and pleuritic chest pain.
- Progressive breathlessness is another presentation.
- At times, the onset is less acute with mild chest pain, low-grade fever, non-productive cough, weight loss and easy fatigability.
- Pleural friction rub may be audible in the early stages.
- Later, classical signs of pleural effusion develop. The physical signs of pleural effusion are discussed under "pleural effusion".

Investigations

- The total leucocyte count is usually normal, but the ESR may be raised.
- Tuberculin skin test is positive in 90% of cases.
- Sputum (spontaneous or induced) may be positive for acid-fast bacilli even when chest radiograph does not show a parenchymal lesion.
- Radiograph of the chest is characteristic. Large effusions are most dense at the base, obscuring the diaphragm. But the shadow thins out at the top. For a detailed description of the radiological features of pleural effusion, refer "pleural effusion". Approximately 20–30% of patients with tuberculous pleural effusions have co-existing parenchymal disease on chest radiograph.

Diagnostic Thoracentesis

- The fluid is usually amber coloured, but sometimes haemorrhagic.
- The fluid is characteristically an exudate, with a high protein content (>3 g/dL) and predominant lymphocytosis. Patients with symptoms less than 2 weeks in duration are more likely to have predominantly polymorphonuclear leucocytes in their pleural

fluid. If the pleural fluid contains more than 10% eosinophils, diagnosis of tuberculous pleuritis is unlikely unless the patient has a pneumothorax or has had a previous thoracentesis. Similarly, number of mesothelial cells is less than 5% of all cells.

- Films from the centrifuged deposit may rarely demonstrate the tubercle bacilli (<10% of immunocompetent cases).
- Cultures are positive in about 25% of cases.
- Adenosine deaminase (ADA) in pleural fluid:
  - In majority of patients with tubercular pleural effusion, the levels of ADA in the fluid are elevated (>40 U/L). This may be related to an increased activity of T lymphocytes (CD4+) in the pleural fluid.
  - High levels of ADA are also reported in effusions due to rheumatoid arthritis, lymphoma, chronic lymphatic leukaemia, empyema, parapneumonic effusions and mesothelioma.
  - The specificity of raised levels of ADA (above a cut-off value) in diagnosing tuberculous effusion is nearly 0.83 while the reported sensitivity varies between 77% and 100%.
  - Clearly, where the incidence of tuberculosis greatly exceeds any other cause of a lymphocytic pleural effusion (like in India), ADA activity has a high positive predictive value.
  - ADA exists as two isoenzymes: ADA1 and ADA2. ADA1 isoenzyme is found in all cells with the highest activity in lymphocytes and monocytes, whereas ADA2 isoenzyme appears to be found only in monocytes. In tuberculous pleural effusion, ADA2 isoenzyme is considered to be primarily responsible for total ADA activity, while in parapneumonic effusions, the ADA1 isoenzyme is the major isoenzyme of ADA.
- Other tests on pleural fluid:
  - Elevated LDH
  - Marked elevation in the levels of soluble interleukin-2 (IL-2) receptors
  - High levels of interferon-gamma (INF-γ)
  - Detection of mycobacterial DNA by PCR
  - Nucleic acid amplification assays (e.g. GeneXpert) to amplify *M. tuberculosis*-specific nucleic acid sequences with a nucleic acid probe.
- Closed pleural biopsy reveals non-caseating granulomas in 80% of cases. It should also be stained with Z–N stain and cultured for mycobacteria.

Management

- The treatment of tuberculous pleural effusion has three goals: (i) to prevent the subsequent development of active TB, (ii) to relieve the symptoms of the patient, and (iii) to prevent the development of a fibrothorax.
- Therapeutic aspiration of pleural fluid may be necessary in severely symptomatic cases.
- Antituberculous chemotherapy is the cornerstone of management.
- Corticosteroid drugs are useful in reducing the symptoms of toxaemia, but they do not reduce the incidence of pleural fibrosis. Prednisolone is given at a dose of 5 mg four times daily for 2–3 weeks followed by gradual tapering over the next 2–4 weeks.

Q. Write a short note on tuberculosis chemoprophylaxis.

- Two terms are used to describe two different sorts of chemoprophylaxis:
  1. Primary or infection prophylaxis where a drug is given to individuals who have not been infected in order to prevent development of disease (e.g. infants being breast-fed by a sputum-positive mother).
  2. Secondary or disease prophylaxis where the drug is used to prevent development of disease in people who have already been infected.
- Isoniazid is used for chemoprophylaxis at a dose of 5 mg/kg/day (but not exceeding 300 mg/day) orally for a minimum period of 9 months. Other options particularly for HIV patients are isoniazid plus rifampicin at10 mg/kg daily for 3 months or isoniazid at a dose of 15 mg/kg (adults 900 mg) plus rifampicin at a dose of 10 mg/kg twice weekly for 3 months.
- It is important to exclude active tuberculosis by history, physical examination, chest radiograph and, if necessary, by other tests before commencing chemoprophylaxis.

Indications

- Breast-fed infants of sputum positive mothers.
- Close contacts of aged 5 years or below who have a strongly positive tuberculin test—an age group liable to suffer from tuberculous meningitis or miliary tuberculosis.

- Newly infected patients as shown by recent change in tuberculin test from negative to positive.
- Certain clinical states in which tuberculosis is more likely to develop—e.g. HIV infection, Hodgkin's disease, prolonged treatment with prednisolone at a dose level exceeding 10 mg/day, leukaemias, severe diabetes mellitus and patients on antimalignancy drugs. If tuberculin test is ≥10 mm (in India), prophylaxis may be offered.

Risks

- Isoniazid resistance can occur if tuberculosis develops despite preventive therapy. It is particularly likely to develop when preventive therapy with isoniazid is inadvertently given to patients with subclinical or unrecognised tuberculosis.
- Hepatotoxicity.

Q. What is bronchopulmonary aspergillosis? How do you classify bronchopulmonary aspergillosis?

- Bronchopulmonary aspergillosis includes the bronchopulmonary diseases caused by *Aspergillus* species, the most common being *Aspergillus fumigatus*. Others in the group include *A. clavatus*, *A. flavus*, *A. niger* and *A. terreus*.

Classification

• Endobronchial saprophytic pulmonary aspergillosis	• Intracavitary aspergilloma
• Allergic bronchopulmonary aspergillosis (ABPA; asthmatic pulmonary eosinophilia)	• Chronic necrotising aspergillosis
• Extrinsic allergic alveolitis (hypersensitivity pneumonitis)	• Invasive pulmonary aspergillosis

Q. Discuss the aetiology, clinical features, diagnosis and management of intracavitary aspergilloma (fungal ball).

Aetiology

- An "aspergilloma" is a ball of aspergillus fungus, the most common being of *Aspergillus fumigatus*. Occasionally other fungi (e.g. *Zygomycetes* and *Fusarium*) may also produce fungal ball.
- An intracavitary aspergilloma can develop in any area of damaged lung where there is a persistent abnormal cavity. The common predisposing lung conditions are tuberculous cavity (most common), abscess cavity, bronchiectatic cavity, bronchial cyst, emphysematous bulla and cavitated malignancy.
- Aspergilloma (fungus ball) is composed of fungal hyphae, inflammatory cells, fibrin, mucous and tissue debris.

Clinical Features

- Usually no specific symptoms occur.
- At times, aspergilloma may be responsible for recurrent scanty to massive haemoptysis. Haemoptysis usually occurs from bronchial blood vessels, and may be due to local invasion of blood vessels lining the cavity, endotoxins released from the fungus or mechanical irritation of the exposed vasculature inside the cavity by the rolling fungus ball.
- Systemic features like lethargy and weight loss can occur.

Diagnosis

- Chest radiograph shows a cavity with a tumour-like opacity inside. A crescentic air shadow separates the fungal ball from the upper wall of the cavity. If the radiograph is repeated in a different position, this ball also moves to occupy the dependent portion of the cavity.
- A CT scan is more sensitive in demonstrating the fungal ball.
- Serum precipitins to *Aspergillus fumigatus* can be demonstrated in some patients.

- Microscopic examination of sputum may show fungal hyphae.
- Sputum culture grows the fungus.

Management

- Surgical removal of the aspergilloma in suitable patients.
- If surgery cannot be performed, systemic antifungal therapy using itraconazole may be tried although its value is doubtful.
- Ultrasound or CT-guided injection of amphotericin B into the cavity has been useful in some cases.
- Bronchial artery embolisation to control haemoptysis.

Q. Discuss the aetiology, clinical features, diagnosis and management of invasive pulmonary aspergillosis.

Aetiology

- Invasion of previously healthy lung tissue by *Aspergillus fumigatus*, usually in patients who are immunocompromised either by drugs or disease.

Risk Factors

- Prolonged neutropenia (<500 cells/mm^3 for >10 days) most common
- Haematopoietic stem cell transplantation
- Solid-organ transplantation (particularly lung transplantation)
- Prolonged (>3 weeks), high-dose corticosteroids
- Haematological malignancies
- Cytototoxic therapy
- Advanced AIDS

Clinical Features

- Severe systemic disturbances.
- Acute rapidly progressive consolidation, necrosis and cavitation of the lungs.
  - Copious amounts of purulent sputum, often blood-stained, due to multiple cavities.
  - Fever, dyspnoea and pleuritic pain.
  - Haemoptysis and mild to massive.
- May disseminate and spread haematogenously to other organs, most commonly the brain (leading to seizures, ring-enhancing lesions, cerebral infarctions, intracranial haemorrhage, meningitis and epidural abscess). Less frequently other organs such as skin, kidneys, heart and liver may be involved.

Diagnosis

- Microscopic examination of sputum shows fungal hyphae.
- Positive culture of sputum.
- Demonstration of serum precipitins to *A. fumigatus*.
- Chest X-ray findings are non-specific and include rounded densities, pleural-based infiltrates that are suggestive of pulmonary infarctions and cavitations. Pleural effusion is uncommon.
- Computed tomography of the chest is quite useful in suggesting this diagnosis particularly in neutropenic patients. It shows multiple nodules and the "halo sign" (a zone of low attenuation due to haemorrhage surrounding the pulmonary nodule) in early stages. Another sign seen in late stages is the air crescent sign, which represents crescent-shaped lucency in the region of the original nodule secondary to necrosis.
- Bronchoscopy and BAL. Transbronchial biopsy is of little value and may produce complications.
- Detection of galactomannan antigen in serum. It is a polysaccharide cell-wall component that is released by *Aspergillus* during growth. Serum galactomannan can be detected several days before the presence of clinical signs, an abnormal

chest radiograph or positive culture. This may allow earlier confirmation of the diagnosis and serial determination of serum galactomannan values may be useful in assessing the evolution of infection during treatment.
- Detection of (1→3)-β-D-glucan, a fungal cell wall constituent, in serum. Also positive in other invasive fungal infections.
- PCR to detect *Aspergillus* DNA in BAL fluid and serum.
- Biopsy may be required for confirmation.

Management

- Antifungal therapy with amphotericin (1.0–1.5 mg/kg/day) with or without flucytosine.
- Intravenous voriconazole (6 mg/kg every 12 hours for two doses and then 4 mg/kg twice a day) is better tolerated and probably more efficacious than amphotericin B. The most frequent adverse effect of voriconazole is visual disturbances, described as blurred vision, photophobia and altered colour perception.
- Intravenous echinocandin derivatives such as caspofungin, micafungin and anidulafungin for the treatment of refractory cases or if the patient cannot tolerate first-line agents.
- In less immunosuppressed patients, itraconazole (200 mg twice a day) is useful orally.

Q. Discuss the clinical features, diagnostic criteria and management of allergic bronchopulmonary aspergillosis (ABPA; asthmatic pulmonary eosinophilia).

- Allergic bronchopulmonary aspergillosis (ABPA) occurs in patients with pre-existing bronchial asthma or cystic fibrosis.
- It results from hypersensitivity to *A. fumigatus*, though other species of *Aspergillus* and some other fungi can also cause it.
- The pathogenesis of ABPA is not completely understood. Aspergillus-specific IgE-mediated type I hypersensitivity reactions, specific IgG-mediated type III hypersensitivity reactions and abnormal T-lymphocyte cellular immune responses appear to play important roles in its pathogenesis.
- In ABPA, *Aspergillus* actually grows in the walls of the proximal bronchi and eventually produces proximal bronchiectasis. The patient also develops repeated episodes of eosinophilic pneumonia that is manifested by wheeze, cough, fever and expectoration with sputum containing fungal mycelia.
- As a result of repeated pneumonic episodes, the chest radiographs show fleeting shadows of infiltrates. There may be transient areas of opacification due to mucoid impaction of the airways, which may present as band-like opacities emanating from the hilum with rounded distal margin (gloved finger appearance). The "ring sign" and "tram lines" are radiological signs on chest X-ray and represent thickened and inflamed bronchi. Eventually, the condition leads to central bronchiectasis and progressive pulmonary fibrosis.

Diagnostic Criteria for ABPA

Main diagnostic criteria	Other diagnostic features
- Bronchial asthma - Pulmonary infiltrates - Peripheral eosinophilia >1000/mm^3 - Serum precipitating antibodies to *A. fumigatus* - Elevated serum IgE (>1000 ng/mL) - Central (proximal) bronchiectasis - Immediate wheal-and-flare response to *A. fumigatus*	- Brownish plugs in sputum - Culture of *A. fumigatus* from sputum - Elevated IgE (and IgG) class antibodies specific for *A. fumigatus*

Management

- Oral prednisolone 40 mg daily for 7–10 days followed by gradual tapering to a maintenance dose of 5–10 mg/day for long term.
- Bronchoscopic extraction of the casts in selected cases.
- Oral itraconazole (200 mg twice a day) is helpful in reducing exacerbations and requirement of steroids.

Q. Discuss the aetiology, clinical features, investigations and management of bronchial asthma.

Q. How will you differentiate early-onset (atopic) asthma from late-onset (non-atopic) asthma?

Q. Discuss the clinical presentation and management of severe acute asthma (status asthmaticus).

Definition

- Bronchial asthma is a heterogeneous disease, usually characterised by chronic inflammatory disease of the airways. It is defined by history of dyspnoea, cough, chest tightness and wheezing, that vary over time and in intensity, together with variable expiratory airflow limitation. It results from narrowing of the airways produced by a combination of muscle spasm, mucosal oedema and viscid bronchial secretion. The airflow limitation is generally reversible spontaneously or with treatment.
- Asthma is usually associated with bronchial hyper-reactivity so several stimuli.
- Asthma-COPD overlap syndrome is characterised by persistent airflow limitation with several features usually associated with asthma as well as COPD.

Classification

- Bronchial asthma can be classified into two main groups or phenotypes:
  1. Early-onset asthma (atopic, allergic and extrinsic).
  2. Late-onset asthma (non-atopic, idiosyncratic and intrinsic).

Features

Early-onset (atopic) asthma	Late-onset (non-atopic) asthma
• Early age of onset	• Late age of onset
• Atopic individuals	• Non-atopic individuals
• External allergens have strong role	• External allergens have no role
• Positive personal and/or family history of allergic diseases like rhinitis, urticaria and eczema	• Negative personal and/or family history of allergic diseases
• Increased levels of IgE in the serum	• Normal levels of IgE in the serum
• Positive skin hypersensitivity tests	• Negative skin hypersensitivity tests
• Positive response to provocation tests	• Negative response to provocation tests
• Responds well to inhaled corticosteroids	• Often requires higher doses of inhaled corticosteroids

Note that this classification is broad and by no means are the features described absolute. In fact, a great degree of overlap exists between these two types

- Other groups of bronchial asthma include non-allergic asthma (often responds less to inhaled corticosteroids) and asthma with fixed airflow limitation (which develops in some patients with long-standing asthma).

Aetiopathogenesis

- Pathogenesis of asthma involves two major factors:
  1. Bronchial hyper-responsiveness.
  2. Inflammatory reaction within bronchial wall.

Role of Allergens

- The allergens responsible for asthma enter the body through various routes:
  - Inspired air (house dust, pollen, feather, animal dander, fungal spores, etc.).
  - Ingestion (allergens in fish, egg, milk, yeast and wheat).

- Previous exposures to these allergens will have stimulated the formation of IgE. Hence, subsequent exposure to these specific allergens will result in an anaphylactic antigen–antibody reaction in the bronchi. This causes the release of pharmacologically active substances from cells in the bronchial wall, which provoke bronchial constriction and inflammatory reaction, leading to symptoms.

Pathogenesis

- Pathogenesis of asthma is complex and not fully understood. It involves a number of cells, mediators, nerves and vascular leakage. The airway inflammation is a chronic inflammation driven by CD4+ cells which leads to IgE synthesis through production of interleukin-4 (IL-4) and eosinophilic inflammation through IL-5.
- Mast cells:
  - Increased in both respiratory epithelium and surface secretions of asthmatics.
  - These cells can generate and release powerful mediators acting on smooth muscles and blood vessels. These mediators include histamine, prostaglandin D_2 (PGD_2) and cysteinyl leucotrienes [leucotriene C_4 (LTC_4), leucotriene D_4 (LTD_4) and leucotriene E_4 (LTE_4)] which cause the immediate asthmatic reaction.
  - Mast cells are activated by allergens through high-affinity IgE receptors as well as by osmotic stimulus (which account for exercise-induced asthma, more appropriately called exercise-induced bronchoconstriction—defined as transient narrowing of lower airway following exercise in the presence or absence of clinically recognised asthma).
    - They also release IL-4, IL-5 and IL-13. IL-4 and IL-13 help in switching of antibody production by B cells to IgE type. In addition, mast cells also secrete tumour necrosis factor-alpha (TNF-α), which may promote neutrophilia after allergenic stimulation. Conversely, mast cells also help limit airway damage. Mast-cell-derived tryptase can cleave IgE, thereby preventing further mast cell activation and helping to contain the allergic response.
- Eosinophils release LTC_4 and basic proteins such as major basic protein, eosinophilic cationic protein and peroxidase that are toxic to epithelial cells. IL-5 has a key role in the modulation of eosinophil differentiation and promotion of eosinophil survival.
- Macrophages play a role in the initial uptake and presentation of allergens to lymphocytes. They are stimulated by low-affinity IgE receptors and release prostaglandins, thromboxane, LTC_4, LTB_4 and platelet activating factor (PAF).
- T-lymphocytes release IL-3, IL-4, IL-9 and IL-13 which activate mast cells. IL-3, IL-5 and other factors activate eosinophils. Secretion of IL-4 helps in switching of antibody production by B cells to IgE type. An increase in Th2 cell activity occurs in asthma.
- Basophils have a crucial role in initiating allergic inflammation through the binding of antigen-specific IgE antibodies.
- Dendritic cells sample allergens from the airways and migrate to regional lymph nodes where they stimulate production of Th2 cells from naïve cells.
- All these mediators lead to inflammation, oedema, hypertrophy of mucus-producing glands and bronchial constriction.
- A summary of cells and mediators involved in the pathogenesis of asthma and some of the trigger factors is shown in the following boxes:

Cells Involved in the Release of Mediators

Important	Less important
• Mast cells	• Neutrophils
• Macrophages	• Platelets
• Eosinophils	• Epithelial cells
• Lymphocytes (Th2 lymphocytes)	

Mediators of Bronchial Hyper-Responsiveness and Inflammation

• Histamine	• Adenosine
• Prostaglandins (PGD_2, $PGF_2\alpha$ and PGE_2)	• Substance P
• Thromboxane	• Oxygen radicals

- Leucotrienes (LTB$_4$, LTC$_4$, LTD$_4$ and LTE$_4$)
- Platelet activating factor (PAF)
- Bradykinin
- TNF-α, IL-4, IL-5, IL-13

- Complement fragments
- Serotonin

Triggering Factors of Asthma

- Exercise (exercise-induced asthma)
- Hyperventilation
- Cold air
- Tobacco smoke

- Dust and acrid fumes including occupational sensitisers
- Respiratory viral infections
- Emotional stress
- Aspirin, β-blockers

Summary of Pathogenesis of Asthma

```
     Cells                              Triggers
       |                                   |
       v                                   v
   Mediators                          Bronchial
       |                          hyper-responsiveness
       v
  Inflammation
       |
       v
            Symptoms
```
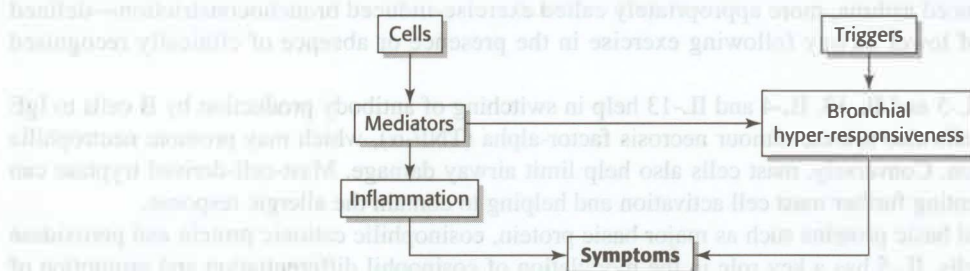
Clinical Features

- Clinical features are conveniently discussed under three headings:
  1. Episodic asthma.
  2. Severe acute asthma (status asthmaticus).
  3. Chronic asthma.
- In general, atopic individuals develop episodic asthma and non-atopic individuals develop chronic asthma.

Episodic Asthma

- Occurs as episodes with asymptomatic intervening periods.
- Characterised by paroxysms of wheeze and dyspnoea with relatively sudden onset.
- Episodes may be spontaneous in onset or triggered by allergens, exercise or viral infections.
- Attacks may be mild or severe and may last for hours, days or even weeks.

Severe Acute Asthma (Status Asthmaticus)

- It is a condition in which severe airway obstruction and asthmatic symptoms persist despite the initial administration of standard acute asthma therapy.
- Severe dyspnoea and unproductive cough.
- Patient adopts an upright position fixing the shoulder girdle to assist the accessory muscles of respiration.
- Physical signs include sweating, central cyanosis, tachycardia and pulsus paradoxus.

Chronic Asthma

- Symptoms are usually chronic unless controlled by appropriate therapy.
- Symptoms like chest tightness, wheeze and breathlessness occur on exertion.
- Episodes of spontaneous cough and wheeze occur during the night.
- Repeated attacks of "severe acute asthma" are common.

- Chronic cough with mucoid sputum, punctuated by recurrent attacks of purulent expectoration from frank infection, is a common feature of chronic asthma. At times, it becomes difficult to distinguish it from chronic bronchitis.

Physical Signs in the Chest
- During an attack of asthma, the following signs are detectable:
  - Respiratory rate is increased with the use of accessory muscles of respiration.
  - Breath sounds are vesicular in character with prolonged respiration.
  - Numerous high-pitched polyphonic expiratory and inspiratory rhonchi are audible.
  - During very severe attacks the airflow may be insufficient to produce rhonchi. This results in a "silent chest", which is an ominous sign.
- In between the attacks, the chest is clear and no abnormal physical signs may be detectable.
- Chronic asthmatics usually have some scattered rhonchi always persisting in their chest.

Other Causes of Wheeze

- Cardiac asthma
- Chronic obstructive lung disease
- Recurrent pulmonary emboli
- Endobronchial lesions/foreign body

- Carcinoid tumours
- Eosinophilic pneumonia
- Pulmonary vasculitis

Investigations

- Chest radiography:
  - In an acute attack, lungs appear hyperinflated.
  - In between attacks, lungs look normal.
  - Long-standing cases have hyperinflated lungs indistinguishable from emphysema.
  - Complications like pigeon chest, lobar or segmental collapse, pneumothorax and mediastinal and subcutaneous emphysema may be seen.
- Pulmonary function tests useful in bronchial asthma are FEV_1, VC and PEF.:
  - Estimation of the degree of airflow obstruction.
  - To determine whether and to what extent the airflow obstruction can be relieved by bronchodilators. In adults, an increase in FEV_1 of >12% or >200 mL from baseline 10–15 minutes after inhalation of 200–400 µg of salbutamol is considered a positive bronchodilator reversibility test.
  - To confirm airflow obstruction provoked by exercise, hyperventilation and occupational exposure.
  - To differentiate chronic asthma from chronic bronchitis. In asthma, there is a diurnal variation in PEF, the lowest values being recorded in the mornings ("morning dipping").
  - Long-term monitoring of patients with poorly controlled disease.
  - Direct challenge tests: Histamine or methacholine provocation test (fall in FEV_1 by more than 20% after provocation with these agents) indicates presence of airway hyper responsiveness and can be useful in patients in whom cough is the only symptom.
  - Indirect challenge tests produce release of endogenous mediators that cause the airway smooth muscle to contract. Commonly available indirect challenge tests include exercise eucapnic voluntary hyperpnoea (EVH), ultrasonically nebulised hypertonic saline and dry-powder mannitol.
  - Pulmonary function tests should be done at diagnosis or start of treatment, after 3–6 months to assess response as well as patient's best FEV_1, and then periodically thereafter.
- ABG analysis shows hypoxaemia and hypocarbia during acute attack. In severe acute asthma, hypercarbia develops.
- Skin hypersensitivity tests check the development of a wheal and flare reaction to intradermal injections of common allergens. The chief value of this is to distinguish atopic from non-atopic subjects (though even this differentiation is not required for management).

- Sputum and blood eosinophilia.
- Elevated serum IgE levels.

Management of Bronchial Asthma

- Goals of asthma management are:
  - To achieve good control of asthma symptoms and maintain normal activities
  - To minimise future risk of exacerbation, fixed airflow limitation and medication side effects
- Management of bronchial asthma can be discussed under following broad headings:
  1. Avoidance of allergens.
  2. Modify risk factors for exacerbation.
  3. Desensitisation or immunotherapy.
  4. Drug therapy to control or suppress clinical manifestations.
  5. Bronchial thermoplasty.

Modify Risk Factors for Exacerbation

- Cessation of smoking; avoidance of passive smoke inhalation.
- Control of associated rhinitis.
- Control obesity.
- Inadequate use of inhaled corticosteroids.
- Avoid overuse of inhaled short-acting beta-agonists (e.g. more than one canister of 200 doses/month).
- Poor inhalation technique.
- Avoid major psychological problems.

Avoidance of Allergens

- In cases where a single allergen is found responsible, it is easy to reduce or avoid the exposure to it.
- In cases where multiple allergens are found responsible avoidance becomes a difficult task.

Desensitisation or Immunotherapy

- Desensitisation is done by repeated subcutaneous injections of gradually increasing doses of the extracts of allergen(s). Its value is doubtful.

Drug Therapy

- The drugs useful in asthma can be grouped into seven major categories. Often, a single drug may not be adequate when a combination of drugs is required:
  1. β-adrenoreceptor agonists.
  2. Methylxanthines.
  3. Corticosteroids.
  4. Chromones.
  5. Anticholinergics.
  6. Leucotriene inhibitors.
  7. Miscellaneous agents.

β-Adrenoreceptor Agonists

- Basically, there are two types of β-adrenoreceptors: β_1-adrenoreceptors and β_2-adrenoreceptors.
  - Stimulation of β_1-adrenoreceptors produces predominant effects on heart.
  - Stimulation of β_2-adrenoreceptors produces predominant effects on bronchial smooth muscles.

Catecholamines

- The useful catecholamines are adrenaline, isoprenaline and isoetharine. Adrenaline is the most commonly used agent in this group. However, it has the disadvantage of not being β_2-selective, which results in significant undesirable cardiovascular side effects. The usual dose is 0.3–0.5 mL of a 1:1000 solution administered subcutaneously which may be repeated thrice at an interval of 20 minutes. It is useful in children.

Salbutamol, Levosalbutamol, Terbutaline, and Fenoterol

- These drugs are highly selective for β_2-adrenoreceptors with their predominant action on the respiratory tract. They are powerful and rapidly but short-acting bronchodilators, which act by relaxing bronchial smooth muscles. They are active by all routes of administration (inhalation, oral, intravenous and subcutaneous), but the preferred route of administration is inhalation. Inhalation is extremely effective, since it rapidly reduces airflow obstruction. Intravenous administration of salbutamol and terbutaline offers no advantages over inhalation. For the same reason, other routes of administration are preferably avoided and reserved for selected indications. Levosalbutamol produces less tachycardia compared to salbutamol.
- For inhalational route, these are available as solutions (for nebulisation), aerosol (metered-dose inhaler or MDI) and dry powder inhaler (DPI).
- Drugs in the MDIs can be dispensed as suspension in chlorofluorocarbons (CFC) or as solution in hydrofluoroalkanes (HFA). Because of impact of CFC on atmospheric ozone, CFC has been replaced by HFA.
- Dose:
  - Salbutamol is given in a dose of 2–4 mg thrice a day orally or two puffs of 100 μg each as required.
  - Terbutaline is given in a dose of 2.5–5 mg thrice a day or two puffs of 100 μg each as required.
  - Levosalbutamol is given in a dose of two puffs of 50 μg each as required.
- Main side effects are tremor and palpitation. Prolonged use of these β_2-adrenoreceptor agonists are preferably avoided as they worsen bronchial hyper responsiveness.

Bambuterol

- It is a long acting β_2-adrenoreceptor agent that gets converted into terbutaline in the body.
- Dose is 10–20 mg once in a day orally.
- Side effects are higher than inhaled β-agonists and include tachycardia, palpitations and tremors.

Salmeterol and Formoterol

- These are highly selective, potent and long-acting β_2-stimulants that need to be given once or twice a day by inhalation (either as aerosol or dry powder).
- These drugs are now routinely used in place of short-acting β_2-stimulants when the patient requires regular β_2-stimulant therapy. However, these drugs should not be used as monotherapy; instead they may be given along with inhaled corticosteroids if response to inhaled corticosteroids is suboptimal.
- Salmeterol has a slow onset of action while formoterol has a rapid action. This makes formoterol suitable for immediate control of symptoms as well.
- Dose:
  - Salmeterol—two puffs of 25 μg each two to three times a day.
  - Formoterol—two puffs of 6 μg each one to three times a day.

Methylxanthines

- These agents have little role as monotherapy but may provide benefit as add-on therapy in patients not controlled with inhaled corticosteroids. However as add-on therapy, methylxanthines are less effective than long-acting inhaled β-agonists.

Theophylline

- Theophylline is a medium-potency bronchodilator, the exact mechanism of bronchodilatation being not clear. It improves the movement of airway mucus, improves diaphragm contractility and decreases the release of mediators.
- Can be given intravenously, orally or as suppository. Therapeutic plasma concentrations of theophylline lie between 10 and 20 μg/mL. However, the dose required to achieve this level varies from patient to patient.
- Acute attacks are treated with short-acting theophylline preparations. For maintenance therapy, long-acting theophylline preparations are used, and are usually given once or twice a day. Single daily dose in the evening is effective in controlling nocturnal asthma.
- Usual dose is 100–200 mg (of plain preparation) three times a day, and 300 mg twice a day or 450–600 mg once a day for sustained-release preparation.

- Common side effects of theophylline preparations include nervousness, nausea, vomiting, anorexia and headache. Seizures and cardiac arrhythmias can occur when plasma levels are more than 30 μg/mL.
- Theophylline (and aminophylline) clearance is reduced in elderly, liver disease, congestive heart failure, and with concurrent use of erythromycin, allopurinol and cimetidine. It is increased with concurrent use of phenytoin and phenobarbitone, and in smokers.

Aminophylline

- Aminophylline is a bronchodilator, which is effective orally, intravenously and as a suppository. The preferred route of administration is intravenous. Intravenous aminophylline therapy may have some role in the management of status asthmaticus (severe acute asthma).
- Aminophylline is given as a loading dose of 5 mg/kg slowly intravenously over 20 minutes. This is followed by a maintenance dose of 0.5 mg/kg/hour given as a continuous intravenous infusion. In those patients who already receiving theophylline, loading dose is preferably withheld or in extreme situations given in a reduced amount at 2.5 mg/kg.
- Rapid infusion of the bolus dose can result in sudden death from cardiac arrhythmias.

Doxophylline (doxofylline)

- Like theopyline, it also inhibits phosphodiesterase leading to increased cyclic 3′, 5′-adenosine monophosphate (cAMP). It has reduced affinity for adenosine A1 and A2 receptors and therefore, has a better safety profile compared to theophylline. It also inhibits PAF-induced bronchoconstriction and subsequent generation of thromboxane A2.
- Dose is 400 mg twice a day.

Corticosteroids

- Corticosteroids are not bronchodilators, but they relieve or prevent airflow obstruction indirectly by their anti-inflammatory effect. They have a beneficial effect on bronchial inflammation and decrease bronchial hyper-responsiveness. They also reverse β_2-receptor downregulation induced by long-term use of β_2-agonists.
- The effects of corticosteroids in acute asthma are not immediate and may not be seen for 6 hours or more after the first dose. Consequently, it is mandatory to continue vigorous bronchodilator and oxygen therapy during this period.
- The vast majority of patients respond to corticosteroids. But there is a minority with little or no response to corticosteroids. They have been labelled corticosteroid-resistant cases.
- Common indications of corticosteroids in bronchial asthma are the following:
  - Acute illness, particularly when not responding to or even worsening despite optimal bronchodilator therapy.
  - Severe acute asthma (status asthmaticus).
  - Corticosteroid inhalers are now the first-line of treatment in all patients who require some antiasthmatic drug regularly. This is because they have their main action on the basic pathophysiology, i.e. they reduce the hyper-responsiveness and inflammation of the bronchial tree.
- Hydrocortisone and methylprednisolone (intravenous) are useful in acute situations. Hydrocortisone is given as a loading dose of 4 mg/kg intravenously followed by 2–3 mg/kg every 6 hours. Methylprednisolone is administered in a dose of 40–125 mg every 6 hours.
- Prednisolone is started as a single daily morning dose of 40–60 mg orally. Thereafter the dose is reduced by half every third to fifth day. An alternate day schedule is preferred where steroid therapy has to be continued for a long time.
- Beclomethasone dipropionate (200 μg), budesonide (200 μg) or fluticasone (125 μg) is given twice daily as aerosols or dry-powder form. Another inhalational steroid is ciclesonide that is given in a dose of 80–160 μg once a day. Others are flunisolide and mometasone. Higher doses may be necessary in severe illness, but not beyond the maximum dose of 2000 μg beclomethasone, 1000 μg fluticasone and 1600 μg budesonide per day. They are relatively free from systemic side effects at the conventional doses. The common side effects are oropharyngeal candidiasis and a husky voice. This can be minimised by the use of a spacing device along with the metered-dose inhaler, and gargling with water after use. Long-term use may produce osteoporosis, skin thinning and adrenal suppression.

Chromones

- Sodium cromoglycate or cromolyn is not a bronchodilator. It inhibits degranulation of mast cells, thereby preventing mediator release. It is only of use in the prophylactic treatment of asthma. Sodium cromoglycate is particularly useful in children with atopic asthma, but may be of some value in a few patients with non-atopic asthma. Therapy is best initiated between attacks or in periods of relative remission. If no response is observed in 4–6 weeks, the drug can be discontinued. Sodium cromoglycate is administered as an inhalation in a dose of 10 mg four times a day.

- Nedocromil sodium acts mainly by inhibiting release of mediators. It is given as an inhalation at a dose of 4 mg two to four times daily. It is of use in the prophylactic control of asthma.
- Ketotifen is not a chromone. It is an antihistaminic that also inhibits release of mediators. It is useful in the prophylactic control of asthma at a dose of 1–2 mg twice daily by mouth. The main side effects are drowsiness and weight gain.

Anticholinergics

- Previously, anticholinergics like atropine sulphate and atropine methyl nitrate were used, but their role is limited by the systemic side effects. The agents currently used are ipratropium bromide and tiotropium. These are non-absorbable quaternary ammonium compounds, relatively free from side effects. These are given as aerosol or in dry-powder form. Ipratropium is also available as nebulisation solution. These agents are particularly useful in two situations:
  1. In patients with co-existent heart disease, in whom methylxanthines and β_2-adrenoreceptor agonists produce significant tachycardia.
  2. In refractory cases, addition of ipratropium bromide or tiotropium enhances the bronchodilator action of β_2-adrenoreceptor agonists.
- Dose:
  - Ipratropium two puffs of 20 μg each four times a day.
  - Tiotropium two puffs of 9 μg each once a day.
  - Ipratropium 250–500 μg nebulisation; may be repeated if required.
- Side effects include dryness of mouth and bitter taste.

Leucotriene Modifiers

- Leucotriene receptor antagonists (montelukast, zafirlukast, and pranlukast) and 5-lipoxygenase inhibitors (zileuton) are useful additive drugs in patients who do not respond to the conventional agents. They are also used in patients who require high doses of inhaled steroids. They can be used as a second choice treatment to inhaled corticosteroids in mild persistent asthma.
- Dose of zafirlukast is 20 mg BID.
- Dose of montelukast is 10 mg once a day in the evening.
- Adverse effects are uncommon and include headache, abdominal pain, skin rashes, angio-oedema, pulmonary eosinophilia and arthralgia. Zileuton can produce liver toxicity.

Miscellaneous Agents

- Proton pump inhibitor (PPI) in patients with symptomatic gastro-oesophageal reflux disease and suboptimally controlled asthma.
- Steroid-dependent patients might benefit from the use of immunosuppressants like methotrexate or gold, but their exact role has not been defined.
- Omalizumab, a recombinant humanised monoclonal antibody against IgE has been shown to be useful in patients with allergic asthma. It blocks circulating IgE binding to receptors on mast cells and basophils, and decreases release of mediators. It is given subcutaneously once every 2–4 weeks. In a small number of patients, it can produce anaphylaxis.

Note

- Avoid opiates, sedatives and tranquillisers in acutely ill asthmatics
- Avoid β-blockers and parasympathetic agonists in asthmatics
- Expectorants and mucolytic agents do not have any significant role in the management of bronchial asthma

Use of an Inhaler

- The canister of inhaler is shaken well
- The patient exhales till functional residual capacity (FRC), i.e. the end of normal expiration

- The nozzle of inhaler is kept near the open mouth; it may also be kept inside the mouth
- The patient activates the inhaler by pressing it and simultaneously inhales rapidly but smoothly till full inspiration
- The breath is held for 10 seconds, and then released
- The patient rinses his mouth with plain water
- The same steps are repeated after 2–5 minutes if the inhaler needs to be taken twice

Spacer

- The spacer is conical in shape and is made of plastic or other materials
- One end of this is attached to the inhaler (after the inhaler has been shaken) and the other end is kept in the mouth
- The patient inhales after activating the inhaler
- Spacers reduce the particle velocity so that less drug is deposited in the mouth; this increases the delivery of drug to the lower airway passages and also reduces the side effects (spacers are quite useful in reducing local side effects of steroids)
- Spacers also diminish the need of coordination between the activation of inhaler and inhalation

Treatment of Exercise-Induced Asthma (Exercise-induced Bronchoconstriction)

- Episodes can be prevented by inhalation of 2 metered doses of salbutamol or terbutaline a few minutes before exercise. However, regular use leads to relative loss of their efficacy.
- Regular treatment with sodium cromoglycate or leucotriene modifiers is often necessary. Additional therapy with an inhaled beta-agonist is often required before exercise.

Bronchial Thermoplasty

- Controlled thermal energy is delivered to the airway wall during a series of bronchoscopies, resulting in a prolonged reduction in airway smooth muscle mass.

Goals of Asthma Treatment

- Asthma is considered to be well controlled when in the last 4 weeks:
  - Daytime symptoms occur twice or less per week.
  - No limitation of daily activities including exercise.
  - No nocturnal awakening due to symptoms.
  - Requirement of short-acting β-agonists twice or less per week.
  - No exacerbations.

Asthma Severity

- Treatment depends on the severity of asthma.

Global Initiative for Asthma (GINA) Severity Grades

Characteristic	Controlled asthma	Partly controlled asthma	Uncontrolled asthma
- Daytime symptoms more than twice/week	No	Any 1 or 2 characteristics present	Any 3 or 4 characteristics present
- Limitation of activities due to asthma	No		
- Nocturnal symptoms/awakening due to asthma	No		
- Need for rescuer medicine more than twice/week	No		

- An additional category is severe asthma.
  - Asthma which requires treatment with high dose inhaled corticosteroids and long-acting beta agonists and/or leukotriene modifier for the previous year or systemic corticosteroids for ≥50% of the previous year to prevent it from becoming uncontrolled asthma or which remains uncontrolled despite this therapy.

Guidelines on the Management of Asthma

- Patient education regarding self-monitoring and correct use of inhalers is important in all patients.

Step-wise approach	Management
• Step 1 (only for intermittent symptoms)	• Short-acting inhaled β₂-agonist on need basis (required in all steps)
• Step 2	• Low-dose inhaled corticosteroids OR • Leucotriene modifiers (if patient develops side effects to inhaled corticosteroids)
• Step 3	• Low-dose inhaled corticosteroids plus long-acting β₂-agonist OR • Medium- or high-dose inhaled corticosteroids OR • Low-dose inhaled corticosteroids plus leucotriene modifiers OR • Low-dose inhaled corticosteroids plus sustained-release theophylline
• Step 4	• Medium- or high-dose inhaled corticosteroids plus long-acting β₂-agonist • May add leucotriene modifiers • May add sustained-release theophylline
• Step 5	• Add oral corticosteroids (lowest dose) • Consider anti-IgE treatment (omalizumab)

- Once patient is on treatment for several months, asthma severity can be assessed using above-mentioned step-wise approach.
  - Mild asthma is well controlled with step 1 or step 2 treatment.
  - Moderate asthma is one which is controlled with step 3 treatment.
  - Severe asthma is that which requires step 4 or 5 treatment to prevent it from becoming uncontrolled asthma.
- Once good symptom control is achieved, the doses of inhaled corticosteroids may be reduced to minimum dose which will maintain asthma control.

Treatment of Severe Acute Asthma (Status Asthmaticus)

Treatment at Home

- High concentrations of oxygen through a mask.
- Bronchodilator therapy with one of the following:
  - Salbutamol (5 mg) or terbutaline (10 mg) by nebuliser every 20 minutes for 3 doses.
  - Salbutamol or terbutaline administered via metered-dose inhalers (four to eight puffs with a spacer every 20 minutes for three doses) has been found to be as efficacious as nebulisation of these agents. These are followed by 4–8 puffs every 2–4 hours.
- If no response within one hour or patient becomes drowsy, shift to a hospital.

Management in Hospital

Initial Assessment and Management

- Take brief history and perform rapid examination.
- High concentration of oxygen (35–60%).

Assessment of Severity

Mild-to-moderate exacerbation
- FEV_1 or PEF $\geq$50%
- Patient talks in sentences
- Pulse $\leq$120 beats/minute
- Minimal or no pulsus paradoxus
- SaO_2 $\geq$90%

Severe exacerbation
- FEV_1 or PEF <50%
- Patient talks in words or phrases but not sentences
- Pulse >120 beats/minute
- Respiratory rate >30 breaths/minute
- Pulsus paradoxus >25 mmHg
- Loud wheezes or silent chest
- SaO_2 <90% or PaO_2 <60 mmHg

Life-threatening asthma
- Drowsy
- Silent chest

Treatment of Mild-to-Moderate Exacerbation

- Inhaled β-agonists (via inhaler or nebuliser) every 20 minutes for 3 doses as discussed above.
- Oral corticosteroids if no immediate response.
- Reassess every hour.

Treatment of Severe Exacerbation

- High concentration of oxygen (35–60%).
- Salbutamol (5 mg) or terbutaline (10 mg) or levosalbutamol (1.25–2.5 mg) nebulised in oxygen should be administered immediately. This may be repeated after a few minutes if there is no response. Subcutaneous or intravenous administration of β₂-agonist is indicated in patients who are coughing excessively, too weak to inspire adequately or moribund. Terbutaline is given subcutaneously (0.25–0.5 mg) or intravenously (0.1–10 µg/kg/minute). Epinephrine (adrenaline) may be given in children and young adults. In adults, the dose is 0.2–0.5 mg as 1:1000 solution subcutaneously every 20 minutes.
- Ipratropium bromide 0.5 mg together with salbutamol 5 mg or terbutaline 10 mg nebulised in oxygen in those patients who do not respond within 15–30 minutes. Can be repeated every 20 minutes for 3 doses. It can also be given by MDI.
- Aminophylline may be given intravenously to those patients who do not respond to nebulised bronchodilators. It is given as a loading dose of 5 mg/kg/hour as an infusion. The loading dose should be avoided in patients who have been given intravenous aminophylline prior to hospital admission and in those who are already on oral methylxanthines. However, addition of aminophylline does not improve outcome as compared to inhaled drugs. In addition, it produces several side effects. Hence, aminophylline is not recommended at present to be used in patients with acute exacerbation.

- Corticosteroids.
  - Hydrocortisone sodium succinate 100 mg intravenously at presentation and then repeated 4–6 hourly in severely ill patients.
  - Oral prednisolone in a loading dose of 40–60 mg and thereafter 40–60 mg/day in single or two divided doses. Total duration is 5–7 days. Patients receiving steroids before should also be given inhaled corticosteroids in high doses.
- Antibiotics are not indicated unless features of respiratory infection are present.
- Role of magnesium sulphate administered intravenously or by nebulisation is controversial.
- Endotracheal intubation and mechanical ventilation in patients who do not respond to above measures. Indications for intubation include cardiac or respiratory arrest, severe hypoxia (PaO_2 <60 mmHg), hypercapnia ($PaCO_2$ >50 mmHg), acidosis (pH <7.3), exhaustion or deterioration in mental status.
- NIV using continuous positive pressure or BiPAP machines and tight-fitting face mask helps in assisting breathing. It reduces the work of breathing without intubation. It is indicated in a cooperative and alert patient who has impending respiratory failure but does not need immediate intubation.
- Treatment with 70–80% helium with oxygen may be beneficial. This mixture reduces airway resistance and improves efficacy of bronchodilators.
- Response to treatment is assessed from patient distress, respiratory rate, FEV_1, heart rate, presence of pulsus paradoxus and serial ABG studies.

Q. Write a short note on occupational asthma.

- Caused by a specific occupational sensitizer
- Occupational sensitisers are usually a protein or glycopeptide which can cause production of specific IgE antibodies and typical allergic responses.
- Examples of allergens include animal allergens, plants and plant products (e.g. natural rubber latex), cereals and grains, milk powder, fungi, diisocyanates (e.g. toluene diisocyanate), acrylic, and drugs.
- Once a person is sensitised, very low exposures can induce asthma.
- A latency period ranging from weeks to years after the first exposure to the sensitiser is often seen before the initial onset of work-related symptoms.
- Symptoms begin variably—at the beginning of work shift, toward its end, or even in the evening after working hours. They subside or improve during weekends and holidays.
- Often associated with allergic rhinitis and conjunctivitis.
- A subcategory of occupational asthma is irritant-induced occupational asthma. In this, occupational asthma occurs from exposure to agents which cause airway irritation with no airway sensitisation.
- Management includes primary prevention (e.g. avoiding use of known sensitising agents if safer alternatives are available, modifying physical or chemical form of known sensitisers to reduce risk of exposure, reducing exposure by means of occupational hygiene measures and educating workers in the use of safe practices at work), secondary prevention (e.g. medical-surveillance programmes for workers at risk, periodic spirometry and early diagnosis) and tertiary prevention (e.g. appropriate treatment).

Q. Discuss the clinical features, diagnosis and management of hypersensitivity pneumonitis (extrinsic allergic alveolitis).

Q. What is meant by farmer's lung?

Definition

- Hypersensitivity pneumonitis or extrinsic allergic alveolitis is an immune-mediated inflammation in the walls of alveoli and bronchioles secondary to inhalation of certain types of organic dusts including microbes (bacteria, fungi or protozoa, including amoebae contaminating water in ventilation systems), animal or plant proteins, and several low-molecular weight chemicals. It is due to T-helper cell-mediated delayed hypersensitivity reaction to inhaled antigens. T helper cells 1 (Th1) release tumour necrosis factor, interferon-alpha, IL-12, and IL-18 while Th17 cell release IL-17 and IL-22.

Examples

Disease	Source of antigen	Putative antigen
• Farmer's lung	Mouldy hay	Thermophilic actinomycetes
• Bird fancier's lung	Avian droppings (most often droppings of pigeons and parakeets)	Protein in avian faeces, feathers
• Mushroom worker's lung	Mushroom compost	Mushroom spores
• Bagassosis	Sugarcane dust	Thermophilic fungi and actinomycetes
• Malt worker's lung	Mouldy barley	*Aspergillus* species
• Maple bark stripper's lung	Maple bark	*Cryptostroma* species
• Humidifier or air-conditioner lung	Contaminated water in air-conditioning systems	*Acanthamoeba, Naegleria,* thermophilic actinomycetes
• Woodworker's lung	Wood dust	Wood dust, *Alternaria* species
• Coffee worker's lung	Coffee bean dust	Antigen unknown
• Miller's lung	Infested wheat flour	*Sitophilus granarius*
• Isocyanate lung	Chemical industries	Toluene diisocyanate
• Hot-tub lung	Contaminated hot tub water or outdoor water pool	*Mycobacterium* (usually *avium*)

- The most commonly implicated bacterial cause is thermophilic actinomycetes, which are Gram-positive filamentous bacilli that produce Farmer's lung.

Clinical Features

- Most patients (80–95%) are non-smokers.
- Most cases occur following months or years of continuous or intermittent inhalation of inciting agent.
- Clinical presentation can be acute, subacute or chronic:
  - Acute form presents as fever with chills, malaise, cough and dyspnoea occurring 6–8 hours after exposure to the antigen. It peaks at 6–24 hours and usually clears off within a few days if there is no further exposure.
  - Subacute form appears more insidiously with cough, dyspnoea and cyanosis, lasting for weeks or months.
  - Chronic form occurs as gradually progressive cough, weight loss and exertional dyspnoea. Clubbing may be present. It usually occurs in patients with continuous low-dose exposure to the antigen and is clinically indistinguishable from pulmonary fibrosis due to other causes.
- Another presentation is acute exacerbation of chronic disease which occurs without further exposure to offending antigen.
- Complications of long-standing disease are diffuse pulmonary interstitial fibrosis, pulmonary hypertension and cor pulmonale.

Investigations

- Blood examination reveals raised ESR and neutrophilia, particularly in acute form. Eosinophil counts and IgE levels are typically normal.
- Precipitating antibodies against offending microbe present in many patients, but their diagnostic utility is limited.
- Chest radiograph may show diffuse micronodular shadowing. Later, reticular shadows due to pulmonary fibrosis occur.
- Computed tomography with high-resolution, shows ground glass opacities, poorly defined centrilobular micronodules and mosaic attenuation or expiratory air trapping, When fibrosis develops, high-resolution CT usually demonstrates reticulation, mainly in the middle portion of the lungs or fairly evenly throughout the lungs but with relative sparing of the extreme apices and bases.
- Pulmonary function tests show a restrictive ventilatory defect with normal FEV_1:VC ratio and reduced diffusion for carbon monoxide. In farmer's lung, most common pattern on PFT is obstructive pattern.

- ABG studies show low PaO_2 and $PaCO_2$.
- Other investigations to confirm the diagnosis include provocation tests, BAL and lung biopsy.
  - Provocation test: Appearance of respiratory or systemic findings, especially fever, 4–10 hours after exposure; leucocytosis; diminished diffusing capacity, diminished VC, or both; increased radiographic abnormalities; worsening alveolar–arterial oxygen pressure difference indicate a positive response.
  - BAL typically shows an increase in the number of T lymphocytes, though some patients may show elevated neutrophils also. BAL lymphocytosis is present when lymphocytes exceed 30% of all cells in non-smokers and 20% in current smokers. Most often, CD4:CD8 ratio is generally below <1 (normal is about 1.8) but it may be as high as 4 which is seen in patients with sarcoidosis.
  - Lung biopsy may show chronic inflammatory cells and poorly defined non-caseating granulomas. In late stages, fibrosis is visible.

Treatment

- Identification and avoidance of the causative antigen.
- Oxygen therapy in severely hypoxaemic patients.
- Prednisolone 1 mg/kg/day orally for 1–2 weeks, followed by gradual tapering over the next 4–6 weeks. Corticosteroids hasten recovery from acute stage, but have no beneficial effects on long-term prognosis.

Q. Discuss the causes, clinical presentation and management of bronchial obstruction.

Causes

• Tumours	Bronchial carcinoma, bronchial adenoma
• Enlarged tracheobronchial lymph nodes	Malignant, tuberculous
• Inhaled foreign bodies	—
• Bronchial casts or plugs	Inspissated mucus, blood clots
• Ineffective expectoration	Collection of mucus or mucopus in the bronchus
• Rare causes	Congenital bronchial atresia, post-tuberculous bronchial stricture, aortic aneurysm, giant left atrium, pericardial effusion

Clinical Features

- Clinical manifestations of bronchial obstruction depend on the following:
  - Whether the obstruction is complete or partial.
  - Presence or absence of secondary infection.
  - Effect on pulmonary function.
  - Cause of obstruction.

Clinical Features Related to Degree of Obstruction

Complete Obstruction

- Air distal to the obstruction is absorbed, alveolar spaces close, and the affected lung tissue becomes collapsed and solidified.
- Physical signs are mediastinal shift to the side of collapse, dull percussion note, and absent or diminished breath sounds.
- Radiological features include mediastinal shift to the same side, elevation of the diaphragm on the same side and a dense pulmonary opacity.
- If the collapse involves a small portion of the lung, mediastinal displacement and abnormal physical signs may be absent, but a characteristic opacity will be seen on the radiograph.

Partial Obstruction

- Results in less resistance to the airflow during inspiration than during expiration. The difference in airflow resistance is accentuated by coughing. The end result is air trapping distal to the obstruction, leading to overdistension of the part of the lung distal to the obstruction (obstructive emphysema).
- Percussion note over such a lesion is hyper-resonant and breath sounds are diminished.
- Radiological examination shows hypertranslucency of the affected part of lung.

Clinical Features Related to Secondary Infection

- Secondary bacterial infection of the lung distal to the obstruction is common. This is usually of low virulence, but in some cases pulmonary suppuration and lung abscess follow.
- Can present with recurrent pneumonia in the same segment/lobe.

Clinical Features Related to Impaired Pulmonary Function

- Symptoms usually follow obstruction of a main or lobar bronchus.
- Sudden occlusion can result in severe breathlessness and hypoxaemia.

Clinical Features Related to the Cause of Obstruction

Tumours

- Bronchial carcinoma produces pulmonary collapse at an early stage. Secondary bacterial infection and empyema are common.
- Bronchial adenoma grows less rapidly and hence complete obstruction and pulmonary collapse are late features. Obstructive emphysema may be seen in the early stages of partial bronchial obstruction.

Enlarged Tracheobronchial Lymph Nodes

- May compress or invade the bronchial wall.
- Clinical manifestations are similar to those seen in tumours.
- Commonest cause is bronchial carcinoma, but less common causes are tuberculosis, Hodgkin's lymphoma and other lymphomas.

Foreign Bodies

- Inhaled foreign body usually gets lodged in the right main, intermediate or lower lobe bronchus. Common foreign bodies inhaled are nuts, peas, beans, small pieces of toys, articles of food and fragments of tooth during dental extractions under general anaesthesia.
- Initial presentation is either as obstructive emphysema or as lobar collapse, with a persistent low-pitched rhonchus (fixed rhonchus).
- Later, there is development of suppurative pneumonia in the collapsed lobe, manifested as high fever, cough with purulent expectoration, pleural pain, pleural rub and signs of either collapse or consolidation.
- Radiological examination may reveal obstructive emphysema or collapse or consolidation.

Bronchial Casts or Plugs

- Mucus plugs cause bronchial obstruction in patients with asthma or pulmonary eosinophilia. Secondary bacterial infection of the collapsed lung may occur.
- Blood clots produce bronchial obstruction following severe haemoptysis.

Retained Secretions

- Bronchial obstruction by retained mucus or mucopus occurs in patients who are unable to cough effectively for some reason.
- Secondary bacterial infection is common and occurs early.

Management

- Identification of the cause by chest radiograph, bronchoscopic examination and biopsy.
- Bronchoscopic removal of the foreign bodies, bronchial casts, plugs and secretions.
- Treatment of the underlying cause.

Q. Define COPD—chronic obstructive pulmonary disease, COLD—chronic obstructive lung disease or COAD—chronic obstructive airway disease.

Q. What are small airway diseases?

Definition

- Chronic obstructive pulmonary disease (COPD), COLD or COAD, is defined as a condition characterised by persistent airflow limitation that is usually progressive and associated with an enhanced inflammatory response in the airway and lungs to noxious gases and partlcies. The major site of obstruction is in the small airways.
- The obstruction is not relieved (improvement <15% of baseline) with bronchodilators.
- Because of associated systemic effects, COPD has been defined as a preventable and treatable disease.
- COPD forms a spectrum with pure chronic bronchitis at one end and pure emphysema at the other end.
- Chronic bronchitis and emphysema are pathologically distinct, but usually co-exist in the same patient in varying proportions.
- Small airways diseases include COPD and asthma. Others include hypersensitivity pneumonitis, bronchiolitis and mineral dust pneumoconiosis
  - Small airways are defined as non-cartilaginous airways with an internal diameter <2 mm. These airways are located from approximately the eighth generation of airways down to the terminal bronchioles and respiratory bronchioles
  - Normally, small airways contribute only a little to total airway resistance.

Q. Discuss the aetiology, pathology, clinical features, course, prognosis and treatment of chronic bronchitis.

Q. Discuss the pathogenesis of the complications of chronic bronchitis.

Q. How do you manage a case of acute exacerbation of chronic bronchitis?

Definition

- Chronic bronchitis is defined as a condition associated with excessive tracheobronchial mucus production to cause cough with expectoration for at least 3 months of the year, for more than 2 consecutive years.

Incidence

- Middle and late adult life.
- More in males than in females.
- More in smokers than in non-smokers.
- More in urban than in rural dwellers.

Aetiology (risk factors)

- Cigarette smoking is the most important risk factor for the development of COPD. However, only about 15 to 20% of smokers develop clinically significant COPD, suggesting that genetic predisposition and environmental factors play a role in the pathogenesis of the disease. Pipe and cigar smokers have increased risk of COPD, although lower than that with cigarette smoking. Cigarette smoking is associated with a variety of abnormalities of the respiratory system. All these abnormalities predispose to the development of chronic bronchitis.
  - Sluggish ciliary movement.
  - Bronchoconstriction (through smooth muscle constriction).
  - Hypertrophy and hyperplasia of mucus-secreting glands. The ratio of thickness of the submucosal glands to that of the bronchial wall is expressed as Reid index (normal 0.44 ± 0.09; in chronic bronchitis >0.51).
  - Release of proteolytic enzymes from polymorphonuclear leucocytes.
  - Release of inflammatory mediators in lungs.
  - Inhibition of the function of alveolar macrophages.
- Air pollution with dust, smoke and fumes, sulphur dioxide and particulate matter. Indoor air pollution, especially from burning biomass fuels (wood, animal dung and crop residues) and coal in confined spaces is associated with increased risk of COPD.
- Occupational hazards as with exposure to dust, smoke and fumes, toluene diisocyanate in plastic industry and carding room workers in cotton mills.

- Familial and genetic factors influence the development of chronic bronchitis:
  - Genetic predisposition.
  - Children of smoking parents.
  - Passive smoking (also known as environmental tobacco smoke).
  - Natural gas used for cooking.
- Previous tuberculosis
- Low socio-economic status.
- Pre-existing asthma may be a risk factor.
- Infections with rhinovirus, *S. pneumoniae*, *H. influenzae* and *Moraxella catarrhalis* can cause exacerbations of chronic bronchitis.
- Exposure to dampness, fog and sudden changes in temperature can cause exacerbations of chronic bronchitis.

Pathogenesis

- Chronic bronchitis and emphysema occur as a result of an inflammatory process involving the airways and distal airspaces.
- Increased activity of oxidants combined with reduced activity of antioxidants has been implicated in the development of inflammation and COPD.
- Cigarette smoke produces high concentration of oxygen free radicals (reactive oxygen species—ROS) including superoxide, hydrogen peroxide and hypochlorous acid. These are responsible for tissue damage and activation of eosinophils and neutrophils. Inflammatory response is initiated through the activation of transcription factors (nuclear factor-κB [NF-κB] and activator protein-1 [AP-1]) and gene expression of proinflammatory mediators.
- Further, cigarette smoke, various oxidants and activated neutrophils damage α-1-antitrypsin that is required to prevent degradation of elastin. All these result in various changes seen in patients with chronic bronchitis and emphysema.
- Various inflammatory mediators involved in COPD include leucotriene B4 (which attracts neutrophils and lympho-cytes), interleukin-8 (which attracts neutrophils and monocytes), TNF-α, IL-1β and IL-6 (which amplify inflammatory response and may be responsible for systemic effects), and transforming growth factor-β (which may induce fibrosis in small airways).
- Pulmonary hypertension develops due to vascular remodelling in COPD, which results from combined effects of hypoxia, inflammation and in severe emphysema, loss of capillaries.

Pathological Changes

- Hypertrophy and hyperplasia of the mucus-producing glands.
- Goblet-cell hyperplasia.
- Reduction in the ciliated cells.
- Mucosal oedema and intraluminal mucus plugs.
- Increased smooth muscle.
- Reduction in the calibre of the air passages.

Clinical Features

History

- The most striking features are an impressive history of cough with sputum production for many years and a relatively late onset of breathlessness.
- Initially, the cough is present only in the winter seasons ("winter cough" or "smoker's cough"), especially in the mornings ("morning cough"). Over years, cough increases in frequency, severity and duration until it is present all round the year.
- The sputum is usually scanty, mucoid and more in the mornings. Sputum is occasionally blood-stained (haemoptysis) and occasionally frankly purulent ("mucopurulent relapse").
- Breathlessness is relatively late in onset in chronic bronchitis. It is due to airflow obstruction and is aggravated by infection, excessive smoking and adverse atmospheric conditions.
- Other symptoms include fever during mucopurulent relapses, wheezing and tightness in the chest.

Modified Medical Research Council (mMRC) Scale for Dyspnea

Grade 0	Gets breathless only on strenuous exercise
Grade 1	Gets breathless when hurrying on level or walking up a slight hill
Grade 2	Walks slower than people of same age on the level because of breathlessness or has to stop for breath while walking at his own pace on the level
Grade 3	Stops for breath after walking 100 meters or after a few minutes on the level
Grade 4	Too breathless to leave the house or gets breathless while dressing or undressing

Physical Signs

- Usually the patient is overweight.
- At rest, there is no respiratory distress. Respiratory rate is normal and accessory muscles of respiration are not acting.
- Percussion note is normally resonant over the lungs. Liver dullness and cardiac dullness are normal in position.

Auscultation

- Vesicular breath sounds with prolonged expiration.
- Inspiratory and expiratory rhonchi.
- Crepitations that either disappear or change in location and intensity after coughing.

Systemic Features

- Decreased free-fat mass.
- Impaired systemic muscle function and muscle wasting.
- Anaemia.
- Osteoporosis.
- Depression.
- Increased risk of angina, acute myocardial infarction and heart failure.
- Metabolic syndrome.

Investigations

- Radiological examination:
  - Chest radiograph does not show any characteristic abnormality in chronic bronchitis.
- Electrocardiography may show features of right atrial and ventricular hypertrophy (tall P waves—P-pulmonale; right bundle branch block; RSR' pattern in V_1).
- Pulmonary function tests:
  - FEV_1 is reduced.
  - FVC is decreased.
  - Ratio of FEV_1 to FVC is subnormal. Presence of post-bronchodilator FEV_1/FVC <70% confirms diagnosis.
  - PEF is reduced.
  - RV is increased.
  - FRC is increased.
  - TLC is increased.
  - Gas transfer may be normal or mildly reduced.
- ABG studies in patients with FEV_1 <50% of predicted, or those with respiratory failure or cor pulmonale.
  - PaO_2 is markedly reduced (hypoxaemia).
  - $PaCO_2$ is markedly raised (hypercarbia).
- Exercise testing:
  - Six-minute walk test used to assess disability and effectiveness of pulmonary rehabilitation.

Complications

Mucopurulent Relapses

- Due to secondary bacterial infection with *S. pneumoniae*, *H. influenzae* or *M. catarrhalis* in 70–75% cases.
- Presents as fever with increased sputum production, which is frankly purulent.

Carbon Dioxide Narcosis

- Persistent CO_2 retention (hypercarbia; high $PaCO_2$) manifests itself as clouding of consciousness, altered behaviour, drowsiness, headache and papilloedema.

Respiratory Failure

- Type I respiratory failure (low PaO_2, normal $PaCO_2$) occurs in mild to moderate disease.
- Acute or chronic type II respiratory failure occurs in severe disease.
- Patient is deeply cyanotic, oedematous and stuporous with respiratory failure.

Secondary Polycythaemia

- This results from the hypoxaemia stimulating erythropoiesis.

Pulmonary Hypertension and Right Ventricular Failure (Cor Pulmonale)

- Pulmonary hypertension results in a chronic afterload on the right ventricle, which hypertrophies and ultimately fails (right ventricular failure; cor pulmonale).
- Manifestations of pulmonary hypertension like visible and palpable pulmonary artery pulsations, sustained left parasternal heave, epigastric pulsations, and a palpable and loud second heart sound may be present.
- Manifestations of right ventricular failure include peripheral oedema, raised JVP, tender hepatomegaly and a third heart sound of right ventricular origin.
- Functional tricuspid regurgitation occurs as a late phenomenon. The manifestations include distended neck veins with large v waves and a rapid descent, and a pansystolic murmur accentuated during inspiration.
- Because of cyanosis (blue) and oedema (bloated up), such patients are referred as blue bloaters.

Pathogenesis of Complications
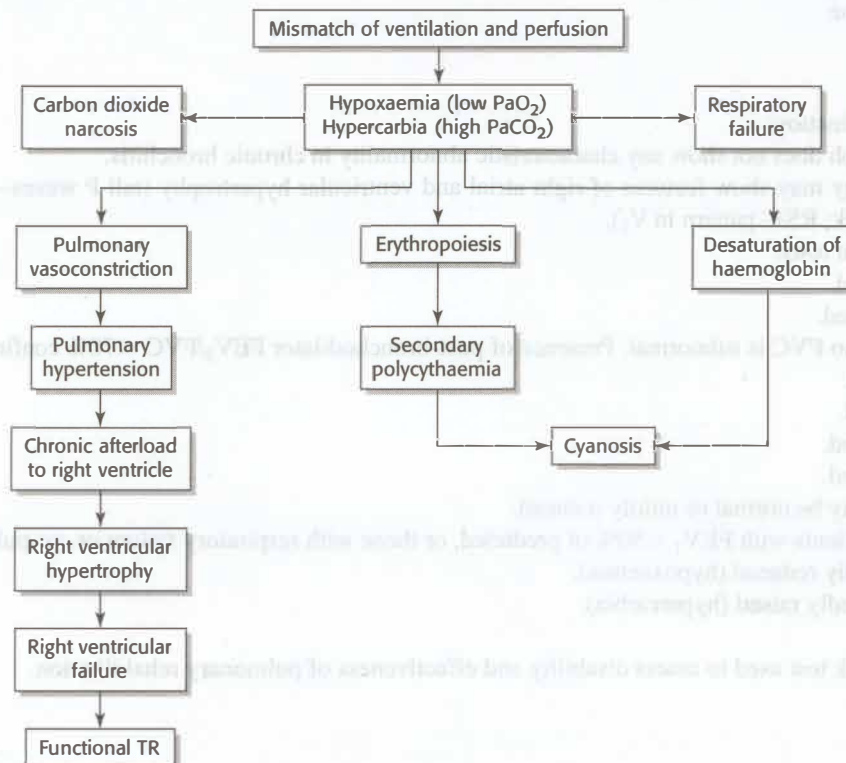
Course and Prognosis (Natural History)

- Chronic bronchitis is a progressive disease characterised by exacerbations and remissions.
- Eventually leads to respiratory and cardiac failure (cor pulmonale).
- Repeated episodes of respiratory and cardiac failure occur, from which prompt recovery occurs with proper treatment.
- Some patients may survive for a few years, while others for many years.

Management

- Regular exercises and nutritional management.
- Weight loss in obese patients.
- Reduction of bronchial irritation:
  - Stop smoking completely. This may be aided by the use of nicotine replacement therapy (by gum, transdermal patch or inhaler) or bupropion, a noradrenergic antidepressant. Bupropion has been shown to be quite effective in this regard. Another drug is varenicline, which is a nicotinic acetylcholine receptor partial agonist. It reduces nicotine withdrawal symptoms. E-cigarettes (electronic cigarettes) have been popularised to help reducing cigarette smoking but these have been found to have several adverse effects and are at present not recommended.
  - Dusty and smoke-laden atmospheres should be avoided.
- Treatment and prevention of respiratory infections:
  - Purulent sputum is treated with oral tetracycline or ampicillin 250 mg 6 hourly or cotrimoxazole 960 mg 12 hourly for 10 days.
  - In the absence of response, sputum culture and sensitivity is done and the antibiotic is changed accordingly.
  - Vaccination with pneumococcal and influenza vaccines.
- Bronchodilator and steroid therapy: None of the existing medications for COPD have been shown to reduce the rate of decline of lung functions. These reduce frequency and severity of exacerbation, and improve health status and exercise tolerance.
  - Inhalation of β_2-adrenoreceptor agonists like salbutamol 200 µg or terbutaline 500 µg 6 hourly in mild to moderate disease. These agents are short-acting and need to be taken frequently. Long-acting β-stimulants (salmeterol and formoterol) are the preferred agents for achieving bronchodilation. These agents may also reduce the incidence of infective exacerbations since these drugs reduce the adhesion of bacteria to airway epithelial cells. Indacaterol (75-300 µg via inhalation) is once a day β_2-agonist with duration of action for 24 hours. Its onset of action is within 5 minutes.
  - Anticholinergic bronchodilator drugs, ipratropium bromide (40–80 µg 6 hourly) or tiotropium bromide (18 µg once a day) should be added in severe disease.
  - Inhaled corticosteroids (beclomethasone, budesonide, fluticasone, ciclesonide) seem to improve airway reactivity and respiratory symptoms and should be added in moderately severe cases.
  - Oral theophylline or doxophylline may be beneficial in selected cases as add-on therapy.
- A new class of drugs is phosphodiesterase 4 inhibitors and includes roflumilast which can be given once a day in combination with inhaled β-agonists, anticholinergics and corticosteroids. Weight loss, diarrhea, headache and sleep disturbances are significant side effect. It should not be comined with theophylline.
- Symptomatic measures:
  - Regular use of antitussives is not recommended to control cough in stable COPD.
  - Hot drinks or steam inhalations to liquefy sputum.
  - Mucolytic agents like bromhexine, N-acetylcysteine, carbocysteine, ambroxol and erdosteine may be tried. Use of mucolytics is associated with a small reduction in acute exacerbations and a reduction in total number of days of disability, but does not alter loss of lung function.
  - Chest physiotherapy.
- Long-term domiciliary oxygen therapy:
  - Long-term, low-dose (2 L/minute) oxygen therapy through nasal cannulae for at least 15 hours a day in patient with:
    - Daytime PaO_2 ≤55 mmHg at rest or oxygen saturation ≤88% with or without hypercapnia confirmed twice over a period of three weeks OR
    - Daytime PaO_2 between 56 and 59 mmHg or oxygen saturation >88% with the evidence of hypoxic organ damage (including right heart failure, pulmonary hypertension or polycythaemia with haemaotocrit >55%).
  - This decreases pulmonary hypertension and prolongs life in hypoxaemic patients who have developed right heart failure. Other benefits include reductions in polycythaemia, pulmonary artery pressures, dyspnoea, hypoxaemia during sleep and reduced nocturnal arrhythmias.

- Treatment of pulmonary hypertension involves long-term oxygen therapy. Use of synthetic prostacyclin (epoprostenol), prostacyclin analogues, endothelin-1 receptor antagonists and phosphodiesterase-5 inhibitors for pulmonary hypertension due to COPD is experimental.
- Pulmonary rehabilitation:
  - The primary goal of pulmonary rehabilitation is to reverse muscular and cardiovascular dysfunction through an individually designed programme.
  - It includes breathing techniques, chest physical therapy, postural drainage, exercise conditioning (upper and lower extremity) and activities of daily living. Also included are evaluation and advice on nutritional needs and psychological and vocational counselling.

Treatment of Severe Acute Exacerbations

- COPD exacerbation is an acute event characterised by worsening of respiratory symptoms with worsening beyond day-to-day variation and leads to change in medication.
- Indicates a combination of increased sputum volume, sputum purulence and increasing dyspnoea.
- Exacerbations increase rate of decline in lung function, deterioration in health status and risk of death.

Oxygen

- Initial therapy should focus on maintaining oxygen saturation at 90% or above.
- This can be achieved by administering oxygen by a nasal catheter or through a face mask equipped to control the inspired oxygen fraction. Venturi masks are the preferred means of oxygen delivery because they permit a precise fraction of inspired oxygen (FiO_2).
- One should be careful while administering oxygen as high flow rates can worsen hypercapnia. Mechanisms proposed to explain this phenomenon are:
  - Increased dead-space due to aggravation of ventilation/perfusion mismatch resulting from the release of hypoxic vasoconstriction.
  - Loss of hypoxic respiratory drive.
  - CO_2 binding capacity decreases as haemoglobin oxygen saturation increases (Haldane effect).

Bronchodilators

- Use of nebulised β-adrenergic agonists (salbutamol 2.5 mg every 20 minutes for initial 1–2 hours) and anticholinergic agents (ipratropium bromide 0.5 mg) improves airflow during acute exacerbations. Both the agents can be combined if required.

Antibiotics

- Indicated in patients with increased dyspnoea, increased sputum volume and increased sputum purulence, or those requiring mechanical ventilation.
- Most common organisms during exacerbations include *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. Risk factors for *P. aeruginosa* infection include recent hospitalisation, frequent antibiotics (four or more courses in last one year) and severe exacerbation.
- For outpatient management, doxycycline, cotrimoxazole or amoxycillin–clavulanate can be given. Patients older than 65 years should also be prescribed one of the newer fluoroquinolones (levofloxacin, gemifloxacin, moxifloxacin).
- Hospitalised patients should receive intravenous antibiotics (azithromycin or fluoroquinolone or a third-generation cephalosporin like ceftriaxone or cefotaxime).
- In severe exacerbations, treatment should include a third-generation cephalosporin plus a fluoroquinolone or an aminoglycoside.

Corticosteroids

- Intravenous or oral corticosteroids should be administered for 5–7 days as they shorten recovery time and improve lung functions (FEV_1) and hypoxaemia.

Aminophylline

- It should be added if the patient fails to respond to initial treatment with nebulisation of β-agonists.

Diuretics

- Diuretics are administered in patients with gross right ventricular failure.

Non-Invasive Positive Airway Pressure Ventilation

- Non-invasive positive pressure ventilation using tight-fitting face mask to deliver BiPAP should be tried when there is a need for ventilatory assistance. It is indicated if patient develops:
  - Acute respiratory acidosis (pH <7.3 and/or PCO_2 >45 mmHg) and/or
  - Severe dyspnoea with clinical signs suggestive of respiratory muscle fatigue, increased work of breathing, or both such as use of accessory muscles of respiration, paradoxical motion of abdomen or retraction of intercostal spaces.
- The patient should be co-operative and medically stable for NIV.

Invasive Ventilation

- If NIV fails or cannot be given, the patient should be intubated for mechanical ventilation.

Indications for Admission

- Marked increase in symptom intensity (e.g. sudden onset of resting dyspnoea).
- New physical findings (e.g. cyanosis and peripheral oedema).
- Severe underlying COPD.
- Presence of important co-morbidities (e.g. cardiac disease).
- New arrhythmias.
- Older age.
- Failure to respond to initial medical treatment.
- Diagnostic uncertainty.
- Insufficient home support.

Management of Associated Co-Morbidities

- It is important to manage co-morbidities as they contribute to mortality and hospitalisation.

GOLD Staging of COPD and Management (Valid for both Chronic Bronchitis and Emphysema)

- Global Initiative for Chronic Obstructive Lung Disease (GOLD) is the global strategy for the diagnosis, management and prevention of COPD. The staging system and management guidelines for COPD are given below:

Stage	Characteristic features*	Management**
I	Mild COPD: FEV_1/FVC <0.70 $FEV_1 \geq$ 80% of predicted	Short-acting β_2-agonists (salbutamol, terbutaline, levosalbutamol) as needed
II	Moderate COPD: FEV_1/FVC <0.70 FEV_1 50–80% of predicted	Long-acting β_2-agonists (salmeterol, formoterol) + anticholinergics (ipratropium, tiotropium)
III	Severe COPD: FEV_1/FVC <0.70 FEV_1 30 to <50% of predicted	Add inhaled glucocorticoids (beclomethasone, budesonide, fluticasone, ciclesonide) + methylxanthines
IV	Very severe COPD: FEV_1/FVC <0.70 FEV_1 <30% of predicted or <50% of predicted with chronic respiratory failure (PaO_2 <90 mmHg with or without $PaCO_2$ >50 mmHg while breathing air at sea level) or cor pulmonale	Add oxygen therapy, ventilatory assistance, management of right-sided heart failure, surgical options

*FEV_1 is post-bronchodilator (e.g. after inhalation of 400 µg of salbutamol)
**Avoidance of risk factors, influenza vaccination and use of short-acting β_2-agonists as needed are common to all stages

Q. What is emphysema? What are the various types of emphysema?

Q. Describe mediastinal emphysema.

Q. What is subcutaneous emphysema?

Q. Discuss compensatory emphysema.

- The word "emphysema" means inflation or distension with air.
- Emphysema can be classified based on the anatomical site:
  - Pulmonary emphysema
  - Mediastinal emphysema
  - Subcutaneous emphysema.

Pulmonary Emphysema

- A detailed description of generalised bilateral pulmonary emphysema is given later. Compensatory emphysema is a form of pulmonary emphysema that is localised.

Compensatory Emphysema

- It is a condition where the normal lung tissue undergoes hypertrophy as a compensatory mechanism for an extensive damage to the other lung or to a part of the same lung.
- Being a compensatory phenomenon, this is asymptomatic.
- Physical findings in compensatory emphysema include reduced respiratory movements, hyper-resonant percussion note and reduced intensity of the breath sounds.

Mediastinal Emphysema

- Mediastinal emphysema occurs as a result of escape of air rapidly into the mediastinum following rupture of overdistended alveoli in severe bronchial asthma, rupture of emphysematous bulla and rupture of oesophagus.
- Air usually tracks upwards into the subcutaneous tissues of the neck where it manifests as "subcutaneous emphysema".
- If severe, mediastinal emphysema may produce cardiac tamponade.
- Auscultation may reveal a crunching sound ("mediastinal crunch").

Subcutaneous Emphysema

- Subcutaneous emphysema is due to the presence of air in the subcutaneous tissues.
- Common causes are penetrating chest injuries, fracture of ribs and intercostal tube introduction.
- Clinically, subcutaneous emphysema imparts a characteristic crepitation or crackling sensation on palpation.
- No treatment is indicated as the air will get absorbed slowly. In severe cases, subcutaneous incisions may be made to relieve pressure.

Q. Discuss the aetiology, pathology, clinical features, investigations, complications and management of pulmonary emphysema.

Q. What is α-1 antitrypsin deficiency?

Q. Give a brief account of pulmonary bullae.

Definition

- Emphysema is defined as a distension of the air spaces distal to the terminal bronchiole with destruction of alveolar septa but without obvious fibrosis.

Aetiology

- Smoking:
  - Alveolar macrophages accumulate around the terminal bronchioles and release proteolytic enzymes. Leucocytes release enzymes such as elastase.
  - These enzymes cause enzymatic digestion and destruction of alveolar walls, resulting in emphysema.
- Occupational causes—furnace blowers, goldsmiths, exposure to cadmium.
- α-1 antitrypsin deficiency:
  - Connective tissue of the lung is digested by the proteolytic enzyme "protease" released from leucocytes. α-1 antitrypsin is a protease inhibitor (antiprotease), preventing this proteolytic digestion. Hence, a deficiency or absence of α-1 antitrypsin results in the proteolytic destruction of lung, eventually leading to emphysema.
  - α-1 antitrypsin deficiency is an autosomal recessive disorder.
  - Pathologically, these patients develop severe panacinar emphysema, predominantly at the lung bases.
  - This type of emphysema is rare and occurs in young adults. It manifests as progressive dyspnoea and minimal cough.
  - Other conditions associated with its deficiency include bronchiectasis, hepatic cirrhosis, vasculitis and panniculitis.

Pathology

- Pathologically, emphysema can be classified into three types according to the pattern of involvement of acini:
  1. Centriacinar (centrilobular) emphysema, where distension and destruction are limited to the respiratory bronchiole and the alveoli closely related to them (central involvement of the acinus with sparing of the periphery). It is the primary pathologic subtype associated with cigarette smoke–induced COPD. This pattern of emphysema is typically more prominent in the upper lung zones.
  2. Panacinar emphysema, where there is generalised destruction of alveoli (both central and peripheral portions of the acinus involved). It is classically associated with α-1 antitrypsin deficiency and is more prominent in the lower lung zones.
  3. Paraseptal emphysema, where distension involves only the distal acinus. It is found near the pleura and may cause spontaneous pneumothorax.

Clinical Features

History

- The most striking feature is steadily progressive exertional breathlessness with minimal cough and expectoration.
- Breathlessness is insidious in onset, initially only exertional, but gradually and steadily progressive, ultimately ending in breathlessness on trivial exertion and even at rest.
- Cough with expectoration of scanty mucoid sputum is characteristically minimal.
- Weakness, anorexia, lethargy and weight loss can occur with advanced disease.

Physical Findings

Inspection and Palpation

- Body build is asthenic.
- Neck is short and thick.
- Neck veins may distend during expiration, but they collapse briskly during inspiration.
- Patient sits leaning forwards, extending the arms to brace himself.
- Patient appears distressed and tachypnoeic.
- Accessory muscles of respiration (sternomastoid and scalene muscles) are hypertrophied. They lift the sternum in an anterosuperior direction during inspiration.
- Prolonged expiration through pursed lips ("pursed lip breathing").
- Expiration begins with a grunting sound.
- Exaggerated tracheal descent during inspiration (Campbell's sign).
- Reduction in the length of trachea above the suprasternal notch.
- Apical impulse is usually invisible or feeble.

- Excavation of the suprasternal and supraclavicular fossae during inspiration.
- Indrawing of the costal margins during inspiration.
- Chest appears cylindrical or barrel like ("barrel-shaped chest"). Anteroposterior diameter of the chest is markedly increased, and the normal ratio of anteroposterior to transverse diameter of 5:7 is altered.
- Whole of the chest is in a fixed state of full inspiration.
- Sternum is arched forwards and angle of Louis is unduly prominent.
- Subcostal angle is widened (normal: 70°).
- Ribs are placed more horizontally and widely.
- Kyphosis of the thoracic spine.
- Chest expansion is symmetrically diminished.

Percussion

- Hyper-resonant percussion note over the lungs.
- Cardiac dullness is reduced or obliterated.
- Liver dullness is pushed down or absent.

Auscultation

- Intensity of the breath sounds is diminished.
- Breath sounds are vesicular in character with prolonged expiration.
- Scattered, faint, high-pitched, end-expiratory rhonchi may be audible.

Investigations

- Radiological features of pulmonary emphysema on chest radiograph PA view are the following:
  - Bullae.
  - Low set, flat diaphragm.
  - Unusually translucent lung fields.
  - Loss of peripheral vascular markings.
  - Widely placed and horizontal ribs.
  - Long and narrow heart ("tubular heart").
  - Prominent pulmonary artery shadows at the hilum.
- Chest radiograph lateral view may show a large retrosternal translucency.
- Computed tomography of the chest can detect emphysema with certainty.
- Pulmonary function tests:
  - FEV_1 is decreased.
  - FVC is decreased.
  - FEV_1:FVC ratio is reduced.
  - PEF is reduced.
  - TLC is increased.
  - RV is increased.
  - RV:TLC ratio is increased.
  - Gas transfer factor for carbon monoxide (diffusion) is reduced.
- ABG studies usually reveal a slightly reduced PaO_2 and normal or mildly elevated $PaCO_2$.

Complications

Pulmonary Bullae

- Bullae are inflated thin-walled spaces created by the rupture of alveolar walls.
- Bullae may be single or multiple, large or small.
- They are usually located subpleurally and along the anterior borders of lungs.
- A subpleural bulla can rupture causing spontaneous pneumothorax.
- Large bullae can interfere with pulmonary ventilation.

Respiratory Failure

- Type I and type II respiratory failure can occur as a late complication of emphysema.

Pulmonary Hypertension and Right Heart Failure

- These are late complications in emphysema.
- The occurrence of right ventricular failure in emphysema is usually a terminal event.

Weight Loss

- Severe weight loss leading to emaciation can occur. This is probably due to impaired testosterone secretion.

Course and Prognosis (Natural History)

- Pulmonary emphysema progresses steadily and gradually as breathlessness with minimal cough and expectoration. Patients are less prone to mucopurulent relapses. Right-sided heart failure and hypercapnic respiratory failure are often terminal events. In the absence of such events, the clinical course is characterised by severe and progressive dyspnoea for which little can be done.

Treatment

- There is no specific treatment for established generalised emphysema. At the most, one can prevent its further progression, and treat the aggravating factors and complications.
- Prevention of progression of emphysema includes cessation of smoking and avoidance of occupational exposure.
- Treatment of aggravating factors and complications include prompt treatment of infections, respiratory failure and right heart failure.
- A trial with bronchodilators and steroids is given, though it may not be successful in patients with pure emphysema.
- Physiotherapy aids in relaxation of cervical muscles and help the patients to exhale slowly and steadily through the pursed lips. It can also facilitate expectoration.
- Surgical ablation of giant bullae may bring about dramatic improvement in pulmonary function.
- Lung volume reduction surgery reduces hyperinflation of one or both lungs by surgical and/or laser resection. This makes respiratory muscles more effective pressure generators due to improved efficiency.
- Heart and lung transplantation may be considered in young patients with severe emphysema due to α-1 antitrypsin deficiency.
- For patients with α-1 antitrypsin deficiency, intravenous replacement therapy using α_1-antitrypsin derived from pooled human plasma is being used but its efficacy is not clear.

Q.   What are blue bloaters?

- This is a distinctive clinical pattern seen in chronic bronchitis.
- Marked cyanosis ("blue") and peripheral oedema ("bloated") are dominant.
- These patients have prominent cough with expectoration, mucopurulent relapses, repeated episodes of right ventricular failure and respiratory failure, arterial hypoxaemia (low PaO_2) and hypercapnia (high $PaCO_2$).

Q.   What are pink puffers?

- This is a distinctive clinical pattern seen in pulmonary emphysema.
- They have marked dyspnoea ("puffer") and no cyanosis (hence "pink").
- The clinical course is characterised by steadily progressive dyspnoea. They maintain a near-normal PaO_2 and $PaCO_2$. The occurrence of respiratory failure and right heart failure are late and often terminal.

Q.   What are the differentiating features of emphysema and chronic bronchitis?

Feature	Emphysema	Chronic bronchitis
Clinical features		
• Dyspnoea	Severe	Mild
• Cough	After dyspnoea starts	Before dyspnoea starts

Feature	Emphysema	Chronic bronchitis
• Sputum	Scanty, mucoid	Copious, purulent
• Mucopurulent relapses	Less frequent	More frequent
• Cyanosis	Absent	Present
• Pulmonary hypertension	Late and mild	Early and severe
• Right ventricular failure	Late and often terminal	Repeated episodes
• Respiratory failure	Late and often terminal	Repeated episodes
Investigations		
• Haematocrit	Normal	Increased
• PaO_2	Normal to low	Low
• $PaCO_2$	Normal	High
• Diffusing capacity	Reduced	Normal
• Chest X-ray	Features of hyperinflation, bullae and tubular heart	Increased bronchovascular markings and cardiomegaly

Q. What are the differentiating features of asthma and chronic obstructive pulmonary disease?

Feature	Asthma	COPD
Age of onset	• Generally, children and young adults	• Generally older people
Risk factors	• Family history of allergies • Allergen exposure • Occupational sensitisers	• Smoking • Occupational exposure • Atmospheric pollution • Alpha-1-antitrypsin deficiency
Respiratory symptoms	• Wheezing, cough, dyspnoea • Symptoms vary from time to time and even over hours or days • May be triggered by exercise, dust or exposure to allergens • Often shows improvement spontaneously or with optimal treatment	• Chronic dyspnoea, productive cough • Usually continuous symptoms • Chronic symptoms usually unrelated to triggers • Slowly progressive symptoms despite therapy
Co-morbidities	• Generally not present	• Often present (e.g. depression, metabolic syndrome, coronary heart disease, osteoporosis, muscle wasting)
Chest X-ray	• Chest X-ray normal	• Shows hyperinflation and other changes
Spirometry	• Reversibility of airway obstruction • Normal between symptoms	• FEV_1 may improve with bronchodilators but $FEV_1/FVC < 0.7$ persists • Persistent airflow limitation
Computerised tomography (if performed)	• May show bronchial thickening	• Emphysema

Q. Describe various components of cigarette smoke.

Q. Name the diseases caused by smoking.

- Cigarette smoke is a complex aerosol composed of gaseous and particulate compounds.
- Smoke consists of mainstream smoke and sidestream smoke components.
  - Mainstream smoke is produced by inhalation of air through the cigarette and is the primary source of smoke exposure for smokers.
  - Sidestream smoke is produced from smouldering of the cigarette between puffs and is the major source of environmental tobacco smoke or second-hand smoke.
- There are more than 4000 chemical constituents of cigarette smoke: 95% of the weight of mainstream smoke comes from more than 400 gaseous compounds; rest of the weight is made up of more than 3500 particulate components.
- Primary determinant of tobacco addiction is nicotine; tar is the total particulate matter of cigarette smoke after nicotine and water have been removed.
- Exposure to tar seems to be a major component of lung cancer risk.
- Mainstream smoke contains many potential carcinogens, including polycyclic aromatic hydrocarbons, aromatic amines, N-nitrosamines and other organic and inorganic compounds, such as benzene, vinyl chloride, arsenic and chromium.

Diseases caused by smoking

- Cancers: Lung, oropharynx, oesophagus, stomach, pancreas, bladder, kidney, cervix, possibly colon and acute myeloid leukaemia.
- Respiratory diseases: COPD, chronic cough and infections.
- Cardiovascular diseases: Coronary artery disease, cerebrovascular disease, peripheral artery disease, abdominal aortic aneurysm.
- Reproductive: Miscarriage, prematurity, low birth weight.
- Gastrointestinal: Gastro-oesophageal acid reflux, peptic ulcer and Crohn's diseases.
- Others: Poor oral and skin health, cataract, fire-related injuries.

Q. Discuss the aetiology, classification, clinical features, investigations, complications and management of bronchiectasis.

Definition

- Bronchiectasis is defined as a permanent abnormal dilatation of one or more bronchi due to the destruction of elastic and muscular components of the bronchial wall.

Classification

1. Saccular (cystic) bronchiectasis:
   - This occurs in the proximal large bronchi.
   - The bronchi show marked dilatation, ending in large sacs.
2. Cylindrical (fusiform) bronchiectasis:
   - This involves the airways from sixth to tenth generation.
   - The bronchi look cylindrical or beaded, and end squarely and abruptly.
3. Varicose bronchiectasis:
   - This is intermediate between saccular and cylindrical changes.
   - The bronchi resemble varicose veins.

Aetiology

• Congenital	Bronchial cysts, α-1 antitrypsin deficiency, cystic fibrosis, primary hypogammaglobu-linaemia, ciliary dyskinesia syndromes (e.g. Kartagener's syndrome), atopic bronchial asthma, pulmonary sequestration
• Acquired (children)	Necrotizing pneumonias (measles, whooping cough, staphylococcus, adenovirus and influenza), primary tuberculosis, foreign bodies
• Acquired (adults)	Pulmonary tuberculosis, suppurative pneumonias, post-obstructive bronchiectasis (endobronchial tumours or foreign bodies, enlarged hilar lymph nodes or tumour masses and bronchostenosis following endobronchial tuberculosis), allergic bronchopulmonary aspergillosis (ABPA), repeated aspiration of gastric fluid, inhalation of toxic gas (ammonia), long-standing asthma and COPD, HIV infection, rheumatoid arthritis, inflammatory bowel disease, Sjögren syndrome, interstitial lung fibrosis (traction bronchiectasis), radiation fibrosis, sarcoidosis, chronic hypersensitivity pneumonitis

Pathology

- Characteristic feature of bronchiectasis is multiple "bronchiectatic cavities".
- Left lung is involved more frequently than the right lung.
- Bronchiectasis can affect any part of the lung, but lower lobes are involved more commonly than upper lobes due to more efficient drainage of the upper lobes by gravity.
- Common sites of involvement are lower lobes, lingula and middle lobe.

Clinical Features

- The hallmarks of bronchiectasis are chronic cough with sputum production, haemoptysis and recurrent pneumonias.
- Cough is chronic and worse in the mornings. It is brought about by postural changes.
- Sputum is characteristically copious, purulent and foul-smelling due to anaerobic infections. Sputum production varies with posture and is maximum in the first 2 hours after waking up.
- If sputum is collected in a conical flask and allowed to stand for some time, it separates into three layers ("three-layered sputum"), a mucoid layer on the top, a mucopurulent layer in the middle and a purulent layer at the bottom.
- Haemoptysis is due to rupture of the thin-walled vessels on the walls of dilated bronchi. It is often recurrent and may vary from slight blood-streaked sputum to massive fatal bleeding.
- Chest pain, which may be pleuritic, is present in 20–30% of patients.
- In widespread bronchiectasis, dyspnoea and wheezing may occur.
- In some cases, the patient is asymptomatic or has non-productive cough ("bronchiectasis sicca"). It commonly occurs following upper lobe tuberculosis.
- Systemic symptoms include fever, weight loss, anaemia, night sweats and weakness.
- Situs inversus in 50% cases of ciliary dyskinesia.
- Acute exacerbation is characterised by increase of sputum with cough, increased dyspnoea, fever, increased wheezing, fatigue and radiological signs of infection
- Recurrent pneumonias are characterised by fever with chills and rigors, night sweats, increased quantity and purulence of the sputum, neutrophil leucocytosis in the blood and radiographic evidence of pneumonia.

Physical Findings

- General examination may reveal anaemia, clubbing of the digits (2–3% cases), fever, halitosis and sinusitis.
- Respiratory signs may be unilateral, but are usually bilateral and basal.
- Presence of large amounts of secretion is responsible for the characteristic "bilateral, basal, coarse, leathery crepitations" of bronchiectasis.
- If the bronchiectatic cavities are dry, there may be no abnormal physical signs.

Investigations

- Blood picture shows anaemia, raised ESR and leucocytosis indicating suppuration.
- In advanced and chronic cases, urine examination may show proteinuria due to renal amyloidosis.
- Sputum studies should include Gram's stain, Ziehl-Neelsen staining for acid-fast bacilli and culture and sensitivity. The culture usually grows normal nasopharyngeal flora. Other commonly grown organisms are *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Pseudomonas aeruginosa* in cystic fibrosis. If sputum cannot be produced spontaneously, sputum induction using hypertonic saline can be done.
- Chest radiograph is usually normal. Cystic or saccular bronchiectasis may be diagnosed by multiple 1–2 cm cystic-appearing lesions with or without fluid levels ("honey comb" appearance or "bird's-nest" appearance). Less often, the chest film shows linear streaks (tram tracks), end on thickened bronchi or signet ring deformity and groups of small curvilinear shadows called grape clusters.
- Electrocardiogram is usually normal, but evidence of right ventricular hypertrophy develops with cor pulmonale.
- Bronchoscopy does not establish the diagnosis. It is indicated in selected situations like identifying the source of secretions, identifying the site of bleeding in patients with haemoptysis and therapeutically to remove secretions.
- Bronchography is rarely indicated presently. Bronchoscopy for bronchoalveolar lavage is reserved for patients who are unable to produce sputum and in whom bacterial infection is suspected or whose CT scan is suggestive of non-tuberculous mycobacterial infection but sputum culture is negative.
- High-resolution computed tomography in which the images are only 1 mm thick, has replaced bronchography for the diagnosis of bronchiectasis.
    - Specific criteria include:
        - Internal diameter of the bronchus is larger than that of its accompanying vessel, or
        - Bronchus fails to taper in the periphery of the chest
    - Besides, some features on CT scan may suggest the aetiology of bronchiectasis (e.g. proximal bronchiectasis suggests ABPA).
- Pulmonary function tests may show obstruction, but a restrictive pattern evolves with advanced disease.
- ABG studies may show respiratory alkalosis or hypoxaemia.
- Measurement of chloride concentrations in sweat is useful in cystic fibrosis. Two sweat chloride levels >60 mmol/L are diagnostic of cyctic fibrosis.
- Immunologic survey is important if primary hypogammaglobulinaemia is suspected.
- Assessment of ciliary function may be done in a number of ways:
    - Assessment of the time taken for a small pellet of saccharin placed in the anterior chamber of the nose to reach the pharynx, where patient can taste it. Normally, it is less than 20 minutes. A prolongation of this time to more than 60 minutes is seen in patients with ciliary dysfunction.
    - Measurement of ciliary beat frequency using biopsies taken from the nose.
    - Electron microscopic study of the ciliary ultrastructure.
    - Study of the sperms.

Complications

- Haemoptysis	- Septicaemia	- Aspergilloma
- Pneumonia	- Osteomyelitis	- Cor pulmonale
- Lung abscess	- Amyloidosis	- Respiratory failure
- Empyema	- Brain abscess	- Hypoproteinaemia

Management

Goals of Treatment

- Treatment of the underlying problems.
- Drainage procedures to improve clearance of tracheobronchial secretions.
- Antibiotics for infections.
- Reversal of airflow obstruction.
- Surgery.

Drainage Procedures

- Nebulisation with 7% hypertonic saline in conjunction with chest physiotherapy.
- Postural drainage consists of adopting a position in which the lobe to be drained is uppermost. Postural drainage should be performed for a minimum of 5–10 minutes twice a day.
- Gentle percussion of the chest wall with cupped hands aids dislodgement of sputum.
- Bronchoscopic removal of inspissated secretions is rarely required.

Antibiotic Therapy

Antibiotics for Eradication of Bacteria

- Pseudomonas and MRSA should be eradicated on first identification with a course of antibiotics
- For Pseudomonas, oral ciprofloxacin 500 mg twice daily or intravenous combination therapy with ceftazidime and an aminoglycoside for two weeks followed by nebulised colistin for 3 months are given.
- For eradication of other pathogenic bacteria in stable patients, antibiotics are given for 5–10 days

Suppressive Antibiotics

- The goal is to reduce bacterial burden for patients in whom eradication of the organism is not successful so as to reduce frequency of exacerbations.
- Inhaled antibiotics are safe and effective in reducing sputum bacterial load. Tobramycin, gentamicin and colistin are antibiotics that are commonly used for nebulisation.

Antibiotics for Acute Exacerbation

- Choice of the antibiotic should primarily be based on the results of culture and sensitivity.
- When no specific pathogen is identified and the patient is not seriously ill, an oral agent like amoxycillin, ampicillin, tetracycline, cotrimoxazole, one of the fluoroquinolones (if tuberculosis has been excluded) or a fixed combination of amoxycillin and clavulanic acid should be used. More seriously ill patients with pneumonitis should be given parenteral antibiotics including anti-pseudomonal coverage.
- Duration of therapy is variable. A 7- to 10-day course is usually sufficient.

Inhibition of Inflammation

- Inhaled corticosteroids
  - Have possible benefit in patients with bronchiectasis.
- Macrolides
  - Have immunomodulatory action.
  - Azithromycin 500 mg thrice a week has been shown to reduce excerbations and sputum production. However, infection with NTM should be excluded before initiating macrolides. Also there is a concern for development of resistant bacteria. Azithromycin may prolong QT interval.

Reversal of Airflow Obstruction

- Bronchodilators to improve obstruction and aid clearance of secretions are particularly useful when some element of reversible airway obstruction is present.
- Inhaled corticosteroids may also be of some use.

Pulmonary Rehabilitation

- May benefit patients with exertional dyspnoea.

Surgical Treatment

- The procedure involved is resection of areas of bronchiectatic lung. Indications of surgery in bronchiectasis are the following:
  - Children or young adults with localised lesions, who do not respond to medical treatment.
  - Recurrent haemoptysis.
  - Recurrent localised pneumonias.
- Lung transplantation in patients with extensive disease and respiratory failure.

Other Measures

- Cigarette smoking should be interdicted.
- A programme of graded exercise, routine deep breathing and maintenance of good nutrition forms essential parts of general management.
- Expectorants and mucolytic agents are of questionable value.
- Episodes of sinusitis should be treated promptly.
- Complicated ABPA should be treated with prednisolone and itraconazole.
- Primary hypogammaglobulinaemia should be treated with human immune globulin.
- Complicated cases may require nasal oxygen on a chronic basis to maintain adequate oxygenation.
- Aerosolised recombinant DNAse has been tried with some success in cystic fibrosis-related bronchiectasis. It reduces the viscosity of sputum by breaking down DNA released from neutrophils.

Prevention of Bronchiectasis

- Adequate treatment and prophylaxis of childhood whooping cough, measles and primary tuberculosis.
- Early recognition and removal of bronchial obstruction.
- Genetic counselling in cystic fibrosis.

Q. What is pseudobronchiectasis?

- A "true" bronchiectasis is not reversible, whereas "pseudobronchiectasis" is reversible.
- The bronchographic abnormalities displayed by atelectasis and tracheobronchitis with ulcerations of the bronchial mucosa simulate cylindrical bronchiectasis. But reexpansion of the collapsed lung in atelectasis and regeneration of the mucosa in tracheobronchitis result in reversibility of the bronchographic appearance. This is known as pseudo-bronchiectasis.

Q. What is post-obstructive bronchiectasis?

- Post-obstructive bronchiectasis is bronchiectasis developing distal to a bronchial obstruction.
- Obstruction of a bronchus results in collapse of the lung and accumulation of secretions distal to obstruction. Secondary bacterial infection supervenes and this results in permanent damage to the distal bronchi resulting in bronchiectasis.
- Since bronchial obstruction is usually confined to one part of bronchial system, post-obstructive bronchiectasis is of the localised variety.
- Post-obstructive bronchiectasis results from obstructions due to endobronchial tumours and foreign bodies, enlarged hilar lymph nodes or tumour masses and bronchostenosis resulting from endobronchial tuberculosis.

Q. What is bronchiectasis sicca (dry bronchiectasis)?

- This is a condition where bronchiectasis presents with repeated episodes of haemoptysis without sputum production.
- This usually occurs in upper lobe bronchiectasis of the post-tuberculous variety.

Q. What is atelectasis? Discuss it briefly.

- The term "atelectasis" describes incomplete expansion or complete collapse of part of the lung parenchyma. This part of lung does not contribute to ventilation and perfusion.

Classification

- Obstructive atelectasis (also known as absorptive atelectasis):
  - Most common type.
  - Results from absorption of gas from the alveoli when communication between the alveoli and major airways is obstructed.

- Intrabronchial obstruction can be exogenous (as in foreign body aspiration, or recurrent aspiration of either gastric or oral contents due to a swallowing disorder), or endogenous (as with tumours, mucus plugging or tracheo- or bronchomalacia).
- Non-obstructive atelectasis:
  - Compression atelectasis:
    - Caused by compression of the lung.
    - Results from any space-occupying lesion of the thorax (e.g. tumours, cysts, enlarged lymph nodes, cardio-megaly), chest wall defects (e.g. scoliosis), neuromuscular diseases and emphesematous bulla compressing on adjacent lung.
  - Relaxation or passive atelectasis:
    - Contact between parietal and visceral pleurae is lost resulting in passive loss of lung volume. Examples include pleural effusion and pneumothorax.
    - Generally atelectasis is due to combined effects of compression and relaxation.
  - Fibrotic or cicatrisation atelecasis:
    - Reduction in volume as a result of parenchymal scarring
- Atelectasis due to surfactant deficiency or dysfunction (adhesive atelectasis):
  - Causes increased alveolar surface tension as well as failure to maintain small airway patency.
  - Results from ARDS (particularly in pre-term neonates and meconium aspiration) and pneumonia in elderly.

Clinical Features

- Depend on the underlying cause, the degree of volume loss within the lung and how quickly the volume loss develops.
- A slowly developing atelectasis of a lobe may produce no symptoms.
- A large atelectactic area of lung may produce features like tachypnoea, tachycardia and cyanosis.
- Chronic atelectasis of any aetiology can become a nidus of chronic purulent infection with bronchial wall damage leading to bronchiectasis.
- Examination may show reduced chest movement during breathing on the involved side, deviation of trachea and apex beat toward affected side, dullness over the involved area and diminished or absent breath sounds.

Investigations

- Chest radiograph and CT chest
  - Opacification of collapsed lobe/segment.
  - Displacement of fissure.
  - Ipsilateral loss of volume with shift of mediastinum and trachea, and elevation of diaphragm and crowding of ribs.
  - Compensatory hyperinflation (visible as hyperlucency) of the remaining lobes
- Arterial blood gas may show hypoxaemia. Hypocapnia may occur due to tachypnoea.
- Bronchoscopy to look for any obstruction. It also helps in removing mucous plug.

Q. Discuss middle lobe bronchiectasis (middle lobe syndrome or Brock's syndrome).

- This is generally a sequel to primary pulmonary tuberculosis.
- Classically, the term middle lobe syndrome is applied to recurrent or chronic atelectasis of the right middle lobe without any endobronchial lesion. However, at present, atelectasis due to endobronchial lesion is also included under this term.
- The most common cause is obstruction of the middle lobe bronchus produced by tuberculous lymph nodes. This is a type of post-obstructive bronchiectasis.
- Due to repeated episodes of atelectasis, bronchiectasis and fibrosis of right middle lobe develops.

Q. Enumerate the clinical features, diagnosis and treatment of ciliary dysfunction syndromes (ciliary dyskinesia syndromes).

Q. Describe primary ciliary dyskinesia (PCD).

Q. What are Kartagener's syndrome and Young's syndrome?

- Ciliary dysfunction syndromes or primary ciliary dyskinesia are a group of genetically determined disorders characterised by dysfunction of cilia of the respiratory tract epithelium, sperms and other cells, causing impairment of mucociliary

clearance, left–right body asymmetry, and impaired sperm motility. Majority are autosomal recessive disorders. Acquired ciliary defects may occur due to infection and inflammation.
- Kartagener's syndrome is one of the ciliary dysfunction syndromes. It is characterised by recurrent sinusitis, bronchiectasis, dextrocardia or situs inversus, and infertility.
- Young's syndrome is characterised by recurrent sinopulmonary infections and obstructive azoospermia.

Clinical Features of Primary Ciliary Dyskinesia

Organ	Clinical manifestations
• Lung	Respiratory distress in neonates Recurrent infections Bronchiectasis
• Sinus	Chronic sinusitis
• Ear	Otitis media Hearing loss Cholesteatoma
• Genitourinary tract	Male infertility
• Organ laterality	Situs inversus totalis Polysplenia or asplenia Complex congenital heart disease Vascular anomalies
• Central nervous system	Hydrocephalus (rare)

Diagnosis

- Screening tests:
  - Low exhaled nasal nitric oxide.
  - Saccharin test—A microtablet of saccharin is placed on the inferior turbinate and the time taken for the subject to taste it is recorded. An abnormal test is any length of time greater than 60 minutes.
- Electron microscopic analysis of respiratory cilia in samples of nasal or airway mucosa reveals defects in the outer or inner dynein arms of the cilia in nearly 70% cases.
- Genetic studies showing mutation in PCD genes.

Treatment

- No specific treatment.
- General treatment of bronchiectasis.
- Cough suppressants should be avoided because cough is the only intact mechanism for mucociliary clearance in these patients.

Q. Define lung abscess. Discuss the aetiology, clinical features, investigations, complications and management of lung abscess.

Definition

- Lung abscess is defined as necrotic area of lung parenchyma containing purulent material.

Aetiology

- Aspiration of nasopharyngeal or oropharyngeal contents (aspiration abscess) is the most common cause.
  - Depression of cough reflex favours aspiration. This occurs during sleep, anaesthesia, alcohol intoxication, epilepsy and coma.
  - Aspiration also occurs in achalasia cardia, carcinoma of oesophagus, hiatus hernia, gastroesophageal reflux disease and large-volume tube feed.
  - Pre-existing sources of infection for aspiration include sinusitis, dental sepsis, gingivitis, periodontal infection, etc.

- Dominant organisms in aspiration abscess include anaerobic organisms (e.g. *Peptostreptococcus, Prevotella, Bacteroides, Fusobacterium*, etc.), streptococci and *H. influenzae*.
- Because of relatively more vertical course of right main bronchus, aspiration abscesses are more common in the right lung.
  - Aspiration abscess cavities are located in those bronchopulmonary segments that are most dependent at the time of aspiration. Aspiration in supine position results in abscess in posterior segment of the upper lobes or superior segments of the lower lobes. Aspiration in the upright position results in abscess in the basilar segments.
- Pulmonary tuberculosis is an important cause of lung abscess.
- Necrotising pneumonias, especially due to *K. pneumoniae, Staph. aureus* and streptococci.
- Bronchial obstruction by foreign body, tumour or bronchostenosis may lead to abscess formation distally.
- Haematogenous spread of the organisms to the lung results from bacteraemia, right-sided endocarditis and septic thrombophlebitis. This often leads to multiple lung abscesses.
- Secondary infection of cavitary malignancy.
- Secondary infection of pulmonary infarct.
- Rupture of amoebic liver abscess into lung.
- Rare causes include pulmonary fungal infections, infected cysts (including hydatid cyst) and vasculitis.

Clinical Features

History

- Lung abscess can have two modes of presentations: acute (<1 month of symptoms) and chronic (>1 month of symptoms).
  - In acute presentation, the disease starts acutely with high-grade fever, chills and rigors, pleuritic chest pain and dry cough. After a few days, when the abscess cavity ruptures into a patent bronchus, the patient suddenly starts expectorating large quantities of sputum. The sputum is large in volume, purulent, foul-smelling and often blood-tinged. The expectoration varies with posture.
  - Lung abscess due to aspiration is often chronic in presentation with insidious onset of low-grade fever, malaise, weight loss, anorexia and a deep-seated chest discomfort. Sputum has putrid smell in many cases.

Physical Findings

- General examination reveals anaemia, fever, finger clubbing, halitosis and oronasal sepsis.
- Respiratory system examination may be normal in the early stages. Later, frank signs of consolidation like dullness on percussion, increased vocal fremitus and vocal resonance, bronchial breathing, crepitations and pleural rub appear. Once the abscess cavity opens into a bronchus, signs of cavitation like cavernous or amphoric bronchial breathing and coarse post-tussive crepitations appear.

Investigations

- Anaemia, leucocytosis and raised ESR.
- Sputum studies should include Gram's stain, Ziehl–Neelsen staining for acid fast bacilli, aerobic and anaerobic cultures and their sensitivity and cytological examination for malignant cells.
- Chest radiograph often shows radiolucency in an opaque area of consolidation. The wall or the border of the cavity completely surrounds the lucent area and an air-fluid level may be seen.
- Bronchoscopy is indicated to exclude malignancy, obtain specimens for studies and for removal of secretions.
- CT scan of thorax can detect lung abscess with certainty.

Complications

• Haemoptysis	• Amyloidosis
• Pleural effusion, empyema	• Aspergilloma
• Pneumothorax, pyopneumothorax and bronchopleural fistula	• Residual fibrosis and bronchiectasis
• Metastatic cerebral abscess	

Treatment

- Postural drainage and chest physiotherapy.
- Antibiotic therapy should be based on sensitivity reports. However, certain broad guidelines may be given:
  - Antibiotic therapy of aspiration abscess is similar to that of aspiration pneumonia.
  - Majority of the patients with lung abscess will respond to oral treatment with ampicillin 500 mg four times daily or cotrimoxazole 960 mg twice daily or clindamycin 300 mg three times a day.
  - In anaerobic bacterial infection (e.g. those with foul-smelling sputum), oral metronidazole 400 mg 8 hourly should be added. It should never be used as a single agent.
  - Seriously ill patients will require parenteral antibiotic therapy in the form of penicillin or clindamycin (600 mg thrice a day) plus metronidazole.
  - Duration of antibiotic therapy is variable. Some patients may require prolonged treatment for 4–6 weeks.
- In large abscess, percutaneous aspiration and placement of pigtail catheters play an important role.
- Resectional surgery is indicated only in selected situations:
  - Massive haemoptysis
  - Localised malignancy
  - Associated symptomatic bronchiectasis
  - Persistent abscess cavity.

Q. Discuss briefly about diffuse alveolar haemorrhage (DAH).

- DAH presents with features of acute- or subacute-onset cough, haemoptysis, diffuse radiographic pulmonary infiltrates, anaemia and hypoxaemic respiratory distress.
- Should be differentiated from localised pulmonary haemorrhage (e.g. due to chronic bronchitis, bronchiectasis, tumour or localised infection)

Causes of DAH

- Can be divided into three groups: those associated with inflammation of the small pulmonary capillaries (capillaritis), those associated with alveolar damage and those without capillaritis or alveolar damage.

With pulmonary capillaritis	Without pulmonary capillaritis and alveolar damage	Diffuse alveolar damage
• Wegener granulomatosis	• Idiopathic pulmonary haemosiderosis	• Any infection causing ARDS
• Microscopic polyangiitis	• Goodpasture syndrome*	• Polymyositis
• Churg-Strauss syndrome	• Systemic lupus erythromatosus*	• Lymphangioleiomatosis
• Systemic lupus erythromatosus*	• Mitral stenosis	• Tuberous sclerosis
• Antiphospholipid syndrome	• Coagulopathy	• Drugs (e.g. amiodarone, cocaine, nitrofurantoin, penicllamine, etc.)
• Mixed cryoglobulinaemia	• Haemangiomatosis	• Pulmonary infarction
• Behcet syndrome	• Infections (e.g. influenza, malaria, dengue, leptospira	• Any cause of ARDS
• Henoch–Schönlein purpura		
• Acute transplant rejection		
• Goodpasture syndrome*		
• Rheumatoid arthritis		

*Can cause DAH due to capillaritis and also without it.

Clinical Features

- Haemoptysis may develop suddenly or over a period of days to weeks. It may be absent in nearly 30% cases.
- Some patients present with severe acute respiratory distress requiring mechanical ventilation.
- Unexplained anaemia.
- Bronchoalveolar lavage reveals several haemosiderin-laden macrophages.
- Clinical features of associated diseases may be present.

Diagnosis

- Hypoxaemia due to impairment of oxygen transfer.
- Elevated diffusing capacity of the lung for carbon monoxide (DL_{CO}).
- Chest radiography shows diffuse alveolar opacities. Recurrent episodes of haemorrhage may produce reticular interstitial opacities due to pulmonary fibrosis.
- CT chest shows bilateral ground glass opacities or consolidation.
- Various blood tests to establish aetiology (e.g. antineutrophil cytoplasmic antibodies, antinuclear antibodies, antiglomerular basement membrane antibodies, antiphospholipid antibodies etc.). Urine may show abnormalities where the disease also invoces kidneys (e.g. Goodpasture syndrome, vasculitides).
- In selected cases, lung biopsy for histopathology.

Treatment

- Establish the underlying diagnosis and treat it.
- Provide respiratory support.
- Prevent progression of microcirculation damage, typically with corticosteroids and immunosuppressive agents.

Q. Classify primary bronchial tumours.

Primary Bronchial Tumours

Benign tumours (5%)	Malignant tumours (95%)
- Pulmonary hamartoma - Bronchial adenoma - Bronchial carcinoid - Cylindroma - Others (chondroma, lipoma)	- Non-small cell carcinoma (75%) - Squamous or epidermoid carcinoma - Large-cell carcinoma - Adenocarcinoma - Bronchioloalveolar cell carcinoma - Small-cell carcinoma (oat cell carcinoma) (25%) - Others - Mucoepidermoid carcinoma - Adenoid cystic carcinoma

Note: Even though carcinoids are classified as benign tumours, some atypical carcinoids behave like low-grade malignat tumours.

Q. Discuss the aetiopathogenesis, histopathological features, clinical features, investigations and management of bronchial carcinoma (bronchogenic carcinoma).

Q. What are the paraneoplastic syndromes associated with bronchogenic carcinoma?

- Bronchial carcinoma is the most common primary malignant tumour of the lung arising from bronchial epithelium or mucous glands.

Incidence

- More common in males than in females.
- Most frequent in 50–75 years age group.
- More in urban than rural dwellers.
- More in smokers than non-smokers.

Aetiology

- Cigarette smoking:
  - Most important cause. The risk is directly proportional to the amount smoked and the tar content of the cigarettes.
  - Cigarette pack-years is calculated by multiplying the number of packs of cigarettes (each containing 20 cigarettes) smoked per day by the number of years the person has smoked.

- Smokers are 40–70 times more prone than non-smokers. Bidi smoking may be more dangerous than cigarette smoking in predisposing to lung cancer. Cigar smoking and pipe smoking are almost as likely to cause lung cancer as cigarette smoking.
  - With comparable amount of smoking, women have higher chances of developing lung cancer than men.
  - The chance of developing lung cancer decreases with cessation of smoking but may never return to the non-smoker level.
  - Second-hand smoke exposure (passive smoking) is also a risk factor.
  - Adenocarcinoma is not related to smoking in many cases. In non-smokers with adenocarcinoma, possibility of other primary sites should be considered.
- Atmospheric pollution in urban areas.
- People who work in asbestos industry.
- Occupational exposure (mining of arsenic, chromium, uranium and nickel and exposure to vinyl chloride).
- Radiation exposure (radon exposure, thoracic radiation therapy). Radon is a gaseous radioactive decay product of uranium.
- Household coal combustion.
- Pre-existing non-malignant lung diseases, such as COPD, idiopathic pulmonary fibrosis and tuberculosis are also associated with increased risk of lung cancer.
- Familial predisposition.

Genetic Mutations

- Mutation in epidermal growth factor receptor (EGFR) tyrosine kinase domain.
- Anaplastic lymphoma kinase (ALK) mutations resulting in its fusion with echinoderm microtubule-associated protein like-4.

Pathology

- To facilitate treatment and prognostic decisions, lung cancer is categorised as small-cell lung carcinoma (SCLC) or non-small-cell lung carcinoma (NSCLC). On the basis of microscopic examination, four major types can be recognised with first three under the category of non-small-cell carcinomas (see classification given earlier).
  1. Squamous (epidermoid) carcinoma.
  2. Adenocarcinoma (including bronchioloalveolar carcinoma).
  3. Large-cell carcinoma. A subtype is large cell neuroendocrine carcinoma which behaves like SCLC.
  4. Small-cell (oat cell) carcinoma.

Note: A new classification given in 2011, has classified lung adenocarcinoma into five types and has eliminated the term bronchioloalveolar carcinoma.

- Squamous cell and small-cell carcinomas are generally centrally placed tumours while large-cell and adenocarcinoma are peripherally placed.
- Neuroendocrine tumours of the lung arise from Kulchitsky cells of the bronchial mucosa and comprise typical carcinoid, atypical carcinoid, small-cell lung cancer and large-cell neuroendocrine carcinoma.
- Treatment decisions are based on whether histologically the tumour is SCLC or one of the NSCLC varieties.

Clinical Features

- Bronchioloalveolar cell carcinoma may present with profuse and mucoid sputum (bronchorrhoea).
- Clinical manifestations of bronchial carcinoma can be considered under the following headings:

Manifestations Due to a Central or Endobronchial Growth

- Cough with haemoptysis.
- Wheeze and stridor.
- Dyspnoea.
- Pneumonitis manifesting as fever and productive cough.

Manifestations Due to a Peripheral Growth

- Chest pain from pleural or chest wall involvement.
- Cough and dyspnoea.
- Symptoms of lung abscess from tumour cavitation.

Manifestations of Regional Spread in the Thorax

- The regional spread of tumour in the thorax may occur by direct extension or by metastasis to regional lymph nodes. The clinical effects of such spread are the following:
  - Haematogenous, lymphatic or direct spread to pleura resulting in malignant pleural effusion.
  - Superior vena caval (SVC) obstruction resulting in SVC syndrome.
  - Tracheal obstruction leading to stridor and dyspnoea.
  - Oesophageal obstruction leading to dysphagia.
  - Recurrent laryngeal nerve involvement with resultant hoarseness of voice and "bovine" cough.
  - Phrenic nerve involvement resulting in dyspnoea and diaphragmatic paralysis.
  - Sympathetic chain involvement leading to Horner's syndrome.
  - Pancoast's syndrome from superior sulcus tumour (refer later).
  - Direct extension to chest wall resulting in rib pain, pathological fractures and intercostal neuralgia.
  - Lymphangitic spread (lymphangitis carcinomatosis) resulting in dyspnoea and hypoxaemia.
  - Pericardial and cardiac involvement with resultant tamponade, arrhythmias or cardiac failure.

Manifestations of Extrathoracic Metastasis

- Brain metastases with headache, vomiting, neurologic deficits, seizures and confusion.
- Bone metastases with pain, pathologic fractures or raised alkaline phosphatase.
- Bone marrow involvement with cytopenias or leucoerythroblastosis.
- Liver metastases resulting in biochemical liver dysfunctions, anorexia, biliary obstruction and pain.
- Lymph node metastases in the supraclavicular region (scalene node).
- Epidural and bone metastases resulting in spinal cord compression syndromes.

Paraneoplastic Syndromes

- Paraneoplastic syndromes are not due to local presence of cancer cells but usually due to humoral factors (hormones or cytokines) secreted by tumour cells or by an immune response against the tumour. These may be the first manifestations of lung cancers. They are often relieved by successful treatment of the primary tumour. Sometimes, these syndromes may be present before a tumour is diagnosed.
- These are common with small-cell carcinoma.

• **Systemic**	Anorexia, cachexia, weight loss, fever
• **Endocrine**	Syndrome of inappropriate secretion of antidiuretic hormone resulting in hyponatraemia (small-cell carcinoma), ectopic ACTH secretion resulting in hypokalaemia rather than full-blown Cushing's syndrome (small cell carcinoma), ectopic production of parathyroid hormone or parathyroid hormone-related peptide resulting in hypercalcaemia and hypophosphataemia (usually squamous cell carcinoma or adenocarcinoma)
• **Skeletal**	Digital clubbing (usually NSCLC), hypertrophic pulmonary osteoarthropathy (usually adenocarcinoma)
• **Neuro-myopathic**	Eaton–Lambert syndrome, limbic encephalitis and retinal blindness (small-cell carcinoma); peripheral neuropathy, subacute cerebellar degeneration, cortical degeneration and polymyositis (all types of lung cancers)
• **Haematological**	Migratory venous thrombophlebitis (Trousseau's syndrome), marantic endocarditis, disseminated intravascular coagulation (DIC), anaemia, granulocytosis, leucoerythroblastosis, eosinophilia, thrombocytosis
• **Cutaneous**	Dermatomyositis, acanthosis nigricans
• **Renal**	Nephrotic syndrome, glomerulonephritis

Lambert–Eaton Syndrome

- An immune-mediated disorder of neuromuscular junction.
- Associated with pre-synaptic voltage-gated calcium channel (VGCC) antibodies.

- Majority cases (50–60%) associated with small-cell lung cancer.
- Clinical triad typically consists of proximal muscle weakness (starting from lower limb and extending to upper limb and later involvement of bulbar and ocular muscles), autonomic features (dry mouth, erectile dysfunction, constipation, orthostatic hypotension), and areflexia. A characteristic phenomenon present in 40% cases is post-exercise facilitation, a short-term return of tendon reflexes and muscle strength to normal after muscle contraction.
- Treatment includes use of 3,4-diaminopyridine, which increases duration of pre-synaptic action potential by blocking potassium efflux, prolonging the activation of VGCC and increasing calcium entry into nerve terminals.

Investigations

- Plain radiograph of the chest may reveal one or more of the following:
  - Peripheral pulmonary opacity with or without cavitation (squamous cell carcinoma may cavitate).
  - Unilateral enlargement at hilum resulting from a central tumour or hilar glandular enlargement or a peripheral tumour in the apical segment of the lower lobe.
  - Bronchioalveolar carcinoma can present as a single mass; as a diffuse, multinodular lesion; or as fluffy infiltrate.
  - Pleural effusion.
  - Collapse of the whole lung, lobe or segment.
  - Mediastinal widening due to mediastinal invasion.
  - Elevation of hemidiaphragm due to pulmonary collapse or phrenic nerve paralysis.
  - Rib destruction from direct extension of tumour or blood-borne metastasis.
- Computed tomography of chest and abdomen is an important investigation for diagnosis and staging of carcinoma. It is useful in several ways:
  - Evaluation of tumour size.
  - Evaluation of mediastinal or hilar lymph node involvement (however, nodal involvement, if seen on CT, should be confirmed by histopathology if the finding will influence therapeutic decisions).
  - To detect pleural extension.
  - To detect occult abdominal disease (e.g. liver and adrenals).
  - For CT-guided biopsy of suspected lesions.
  - To assess the response to treatment.
- Cytological examination of the following specimens may be positive for malignant cells:
  - Sputum
  - Bronchial brushings
  - Bronchial washings
  - Percutaneous needle aspiration biopsy from a peripheral tumour.
  - Fine needle aspiration of lymph node, skin or liver in patients with metastasis.
- Bronchoscopy:
  - Bronchoscopy permits visualisation and biopsy of an intrabronchial tumour.
  - Collection of bronchial washings from the suspicious segments.
- Other investigations useful in diagnosis and staging of disease in appropriate patients are:
  - Scalene node biopsy
  - Mediastinoscopy
  - Pleural aspiration and biopsy
  - Barium swallow.
- Endoscopic ultrasound-guided fine needle aspiration of mass or lymph node.
- Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) helpful in diagnosis of mediastinal, paratracheal and peribronchial lesions, as well as in lymph node staging for lung cancer.
- Ultrasonographic examination of liver and adrenal glands.
- Bone scans if metastasis is suspected.
- Bone marrow trephine biopsies if metastasis is suspected.
- Brain CT if metastasis is suspected.
- PET scan is often used to detect both intrathoracic and metastatic disease. Though CT may be used for mediastinal structures, staging is enhanced by PET. Integrated CT/PET scanners are better than CT or PET alone.
- Molecular testing for EGFR mutations and ALK fusions to guide treatment.

Staging

- Involves extent of tumour (anatomic staging) and assessment of a patient's ability to withstand various treatments (physiological staging).
- The non-small-cell carcinoma is staged into stages I to IV depending on the size and location of primary tumour, involvement of lymph nodes and distant metastasis (TNM International Staging System).
- The small-cell carcinoma is staged into limited-stage and extensive-stage disease based on whether the known tumour can be encompassed within a tolerable radiation therapy port.

Staging of Non-Small-Cell Carcinoma (TNM classification)

TNM	Description
• Tx	Main tumour cannot be assessed, or cancer cells seen on sputum cytology or bronchial washing but no tumour can be found
• T1	Tumour ≤3 cm in diameter; surrounded by lung or pleura; does not invade main bronchus
• T1a	Tumour 2 cm or less in greatest dimension
• T1b	Tumour >2 cm but ≤3 cm
• T2	Tumour >3 cm in diameter; may invade pleura; may extend into main bronchus but remains 2 cm or more distal to carina
• T2a	Tumour >3 cm but ≤5 cm
• T2b	Tumour >5 cm but ≤7 cm
• T3	Tumour >7 cm, invasion of chest wall, diaphragm, pleura or pericardium; main bronchus <2 cm distal to carina; atelectasis of entire lung
• T4	Invasion of mediastinum, heart, great vessels, trachea, oesophagus, vertebral body or carina; separate tumour nodules; malignant pleural effusion
• N0	No nodal metastasis
• N1	Involvement of ipsilateral peribronchial or hilar nodes and intrapulmonary nodes
• N2	Involvement of ipsilateral mediastinal or subcarinal nodes
• N3	Involvement of contralateral nodes or any supraclavicular nodes
• M0	No distant metastasis
• M1	Distant metastasis

Based on TNM classification, the non-small-cell carcinoma can be divided into various stages:

- Occult TxN0M0
- IA T1aN0M0 or T1bN0M0
- IB T2aN0M0
- IIA T1aN1M0 or T1bN1M0 or T2aN1M0 or T2bN0M0
- IIB T2bN1M0 or T3N0M0
- IIIA T1N2M0 or T2N2M0 or T3N1M0 or T3N2M0 or T4N0M0 or T4N1M0
- IIIB T1–4N3M0 or T4N2M0
- IV T1-4N0-3M1

Staging of Small-Cell Carcinoma

Stage	Description
• Limited stage	Disease confined to one hemithorax and regional lymph nodes (including mediastinal, contralateral hilar, and ipsilateral and contralateral supraclavicular)
• Extensive stage	Disease with metastasis beyond ipsilateral hemithorax (including malignant pericardial or pleural effusion)

Functional Evaluation

- Evaluation of performance (Karnofsky performance status; Eastern Co-operative Oncology Group Performance Status) and pulmonary status before discussing the treatment options.
- Pulmonary function tests, specifically FEV_1 and diffusion capacity helpful in predicting morbidity and mortality in patients undergoing lung resection.

Treatment

Non-Small-Cell Carcinoma

- Surgical resection of the tumour is possible, but only in a few selected cases (stages IA, IB, IIA, IIB and selected IIIA).
- Post-operative chemotherapy (adjuvant therapy) is often given to most patients in stage IIA and IIB.
- Pre-operative chemotherapy (neoadjuvant chemotherapy) improves survival in stage IIIA patients. Drugs commonly used are carboplatin, paclitaxel + bevacizumab (an antiangiogenesis drug).
- Treatment for unresectable non-small-cell carcinoma (stage IIIB and IV) involves radiotherapy and chemotherapy. First-line drugs include either cisplatin or carboplatin and one of the taxanes (paclitaxel or docetaxel) or gemcitabine or a vinca alkaloid.
- Targeted therapies, specifically the epithelial growth factor receptor tyrosine kinase inhibitors may increase survival. These include gefitinib, erlotinib and cetuximab. Others include antiangiogenesis agents like bevacizumab and ALK tyrosine kinase inhibitors like crizotinib.
- Radiotherapy is much less effective than surgical therapy. Patients with stage III disease as well as stages I and II disease, who refuse surgery or are not the candidates for pulmonary resection, should be considered for radiation therapy with curative intent. Palliative radiotherapy is indicated in the following situations:
  - SVC obstruction.
  - Recurrent haemoptysis.
  - Painful skeletal metastasis.
  - Tracheal and main bronchial obstruction [neodynamic-YAG (yttrium–aluminium–garnet) laser therapy administered through a flexible bronchoscope can also provide palliation in such patients].
  - Pain caused by chest wall invasion.
  - Pancoast's tumour is usually treated with combined radiotherapy and surgery.

Small-Cell Carcinoma

General Plan of Treatment

- Limited stage with good performance status of patient—Combination chemotherapy with radiotherapy.
- Limited stage with poor performance status—Modified chemotherapy and/or palliative radiotherapy.
- Extensive stage with good performance status—Combination chemotherapy + local radiotherapy.
- Extensive stage with poor performance status—Modified chemotherapy and/or palliative radiotherapy.
- If the patient responds, prophylactic radiotherapy is given to brain. High-dose radiotherapy to the whole brain is also given to patients with documented brain metastasis producing significant symptoms. Prophylactic brain radiotherapy is also considered for reducing CNS metastases in patients with initial partial or complete response.

Chemotherapeutic Regimens

- Commonly used drugs include cisplatin, carboplatin, etoposide, cyclophosphamide, ifosfamide, doxorubicin, vincristine and more recently, topotecan, irinotecan and paclitaxel.
- Commonly used combinations include: cisplatin or carboplatin plus etoposide; ifosfamide, carboplatin and etoposide with or without vincristine; cyclophosphamide, doxorubicin and vincristine; cyclophosphamide, doxorubicin and etoposide; or etoposide, cisplatin and paclitaxel.

Prevention

- Avoidance of risk factors.
- Chemoprevention—use of dietary or pharmaceutical interventions to slow or reverse the progression of premalignancy to invasive cancer. At present, it is in experimental stages. Various agents being studied include retinoids, iloprost (a long-acting oral prostaglandin analogue) and cyclogenase oxidase (COX) inhibitors (e.g. celecoxib). Two agents, vitamin E and β-carotene, actually increase the risk of lung cancer in heavy smokers.

Q. What are the neurological manifestations of bronchial carcinoma?

Regional effects
- Horner's syndrome
- Recurrent laryngeal nerve paralysis
- Phrenic nerve paralysis
- Pancoast's syndrome
- Intercostal neuralgia

Metastatic effects
- Brain
- Spine

Remote effects (paraneoplastic)
- Polyneuropathy
- Myelopathy
- Cerebellar degeneration
- Cortical degeneration
- Polymyositis and dermatomyositis
- Eaton–Lambert syndrome
- Limbic encephalitis

Q. Briefly discuss hypertrophic osteoarthropathy (hypertrophic pulmonary osteoarthropathy).

- Also known as Pierre–Marie–Bamberger syndrome, hypertrophic osteoarthropathy is characterised by periosteal new bone formation, clubbing of digits and arthritis.
- Possible mechanisms suggested invoke stimulation of vagal neural arc and circulating vasodilators, hormones and immune complexes.
- However, studies have suggested a possible role of platelets in the development of clubbing particularly hypertrophic osteoarthropathy. It is postulated that circulating megakaryocytes and large platelet particles, normally destroyed by the lungs, reach distal extremities and interact with endothelial cells resulting in liberation of PDGF and other factors. These factors cause proliferation of connective tissue. Overexpression of vascular endothelial growth factor is also a contributory cause.

Causes

- Any disease-producing clubbing can produce this condition. However, common causes are:
  - Bronchial carcinoma
  - Chronic suppurative lung diseases
  - Chronic liver diseases
  - Metastases to the lung
  - Pleural mesothelioma
  - Cystic fibrosis.
- Primary cause is hypertrophic osteoarthropathy (autosomal dominant).

Clinical Features

- Most commonly involved are the distal parts of the long bones of wrists (radius and ulna) and ankles (tibia and fibula).
- There is pain and swelling of the wrists and ankles, but to a lesser extent in knees and shin also. Pain is aggravated by dependency and relieved by elevation of the limb.
- Examination reveals digital clubbing, swollen and tender joints and pitting oedema of the anterior aspect of shin.
- Radiologically, the distal ends of long bones show periosteal thickening with subperiosteal new bone formation along the shaft. The ends of distal phalanges may show osseous resorption.
- Radionuclide studies of bones reveal pericortical linear uptake along the cortical margins of long bones that may be present before any radiographic changes.

Treatment

- Identification and treatment of the associated disease.
- Vagotomy or percutaneous blocking of the vagus nerve provides relief in some patients.
- Aspirin or other non-steroidal anti-inflammatory drugs and analgesics.

Q. Describe Pancoast's syndrome (Pancoast's tumour; superior sulcus tumour syndrome, Pancoast–Tobias syndrome).

- Pancoast's tumour or Pancoast–Tobias tumour is a tumour of lung apex (superior sulcus tumour). Anatomically, pulmonary sulcus is synonymous with the costovertebral gutter, which extends from the first rib to the diaphragm. The superior pulmonary sulcus describes the uppermost extent of this recess.
- Most cases are NSCLC.
- Local extension of the tumour involves the eighth cervical (C8) and first thoracic (T1) nerves.
- Pancoast's syndrome comprises:
  - Shoulder pain that radiates to neck, axilla, anterior chest wall, medial aspect of scapula, and in the ulnar distribution of arm, i.e. along the C8, T1 distribution. Pain is attributed to invasion of parietal pleura, endothoracic fascia, bony skeleton and brachial plexus.
  - Wasting of the small muscles of the hand from C8, T1 nerve involvement.
  - Pain and tenderness over the first and second ribs and radiological evidence of rib destruction resulting from local invasion by tumour.
  - Horner's syndrome due to involvement of the sympathetic pathway as it passes through T1 root.
  - Upper arm oedema due to invasion and partial or complete occlusion of subclavian vein.
- Cough, dyspnoea and haemoptysis occur less frequently.
- Investigations include CT scan, fine needle aspiration and MRI. MRI is the modality of choice for imaging structures of the thoracic inlet, including brachial plexus, subclavian vessels, spine and neural foramina.
- Treatment is generally combined chemoradiotherapy and surgery. Pre-operative radiotherapy along with chemotherapy (cisplatin and etoposide) is given followed by an en-bloc resection of the tumour and involved chest wall 3–6 weeks later.

Q. Discuss the clinical manifestations and treatment of bronchial adenoma.

- Bronchial adenomas occur in the younger age group, affecting males and females equally.
- These are benign tumours with some properties of malignant tumours, thus requiring surgical removal.
- There are two histological types of bronchial adenoma: the common bronchial carcinoid and the rare cylindroma.
- Recurrent haemoptysis is the most common presentation. Other manifestations include recurrent bronchopulmonary infections and physical signs of collapse. Carcinoid syndrome (cutaneous flush, bronchospasm, diarrhoea and valvular lesions, particularly tricuspid regurgitation) is unusual with bronchial carcinoid; it can occur if hepatic metastasis occurs. On the other hand, this tumour may secrete ACTH causing full-blown Cushing's syndrome.
- Diagnosis can be confirmed by bronchoscopy, biopsy and histology.
- Ideal treatment is surgical resection. When surgical resection is not possible, laser therapy may be tried.

Q. Define mediastinum. What are its various compartments?

- Mediastinum is the region between the pleural sacs.
- It is anatomically defined by the following structures:
  - Thoracic inlet—above.
  - Diaphragm—below.
  - Mediastinal pleura—laterally.
  - Paravertebral gutter and ribs—posteriorly.
  - Sternum—anteriorly.

Compartments

- Based on the lateral chest radiograph, mediastinum can be divided into four compartments:
  1. Superior mediastinum—bounded above by the plane of the first rib and below by an imaginary line drawn anteroposteriorly from the sternal angle to the inferior margin of four thoracic vertebra.
  2. Anterior mediastinum—in front of the heart (extends from sternum anteriorly to pericardium and brachiocephalic vessels behind).
  3. Posterior mediastinum—behind the heart (bounded by pericardium and trachea anteriorly and vertebral column posteriorly).
  4. Middle mediastinum—between the anterior and posterior mediastinum.

Contents of Superior Mediastinum

- Trachea
- Upper oesophagus
- Thymus gland
- Thoracic duct
- Superior vena cava (SVC)

- Arch of aorta and its branches
- Phrenic nerve
- Vagus nerve
- Left recurrent laryngeal nerve
- Lymph nodes

Contents of Anterior Mediastinum

- Thymus gland
- Anterior mediastinal lymph nodes

- Internal mammary artery and vein
- Fatty tissue

Contents of Middle Mediastinum

- Heart
- Ascending aorta
- Arch of aorta
- Vena cavae
- Brachiocephalic arteries and veins

- Phrenic nerves
- Trachea
- Main bronchi
- Hilar lymph nodes
- Pulmonary arteries and veins

Contents of Posterior Mediastinum

- Descending aorta
- Oesophagus
- Thoracic duct

- Azygos vein
- Sympathetic chain
- Lymph nodes

Q. Discuss the causes, clinical features and management of superior vena cava (SVC) syndrome.

- Superior vena cava (SVC) syndrome results from obstruction of SVC secondary to compression and/or invasion by superior mediastinal tumours or other lesions and/or thrombosis of SVC.

Causes of SVC Obstruction

- Bronchial carcinoma (75%)
- Lymphomas (20%)
- Metastatic tumours
- Tuberculosis
- Fibrosing mediastinitis

- Retrosternal goitre
- Thymoma
- Parathyroid tumour
- Aortic arch aneurysm
- Central venous catheter, causing thrombosis

- Note that all the causes listed above other than bronchial carcinoma and lymphoma, are extremely rare.

Clinical Features

- Clinical features due to involvement of other structures of mediastinum may be present (refer mediastinal tumours).
- Clinical features due to involvement of SVC are the following:
  - Headache, visual disturbances and alteration in the state of consciousness (due to raised intracranial pressure).
  - Orthopnea may occur since a supine position will increase the amount of blood flow to the upper torso.
  - Conjunctival oedema, suffusion and subconjunctival haemorrhage.
  - Oedema, swelling and cyanosis of face, neck and upper limbs due to reduced venous flow.
  - Hoarseness, cough, stridor, dyspnea and dysphagia due to oedema of larynx or pharynx.
  - Distended non-pulsatile neck veins.
  - Dilated veins on the upper thorax and upper limbs.

Features Based on Location of SVC Obstruction

Pre-Azygous or Supra-Azygous

- Obstruction of blood return above the entrance of azygous vein into the SVC results in venous distension and oedema of the face, neck and upper extremities.

Post-Azygous or Infra-Azygous

- Obstruction below the entrance of azygous vein into the SVC results in retrograde flow through the azygous via collaterals to the inferior vena cava, resulting in not only the symptoms and signs of pre-azygous disease but also dilation of the veins over the abdomen. This is usually more severe and poorly tolerated than pre-azygous obstruction.

Diagnosis

- It is based on clinical features.
- Chest radiograph shows widening of the superior mediastinum, most commonly on the right side. Pleural effusion may be seen in 25% cases. Rarely, the chest radiograph may be normal.
- CT of the chest provides the most important view of the mediastinum.
- MRI and MR angiography
- Invasive procedures like bronchoscopy, percutaneous needle biopsy, mediastinoscopy and thoracoscopy can be performed by a skilled clinician, though there is some danger of bleeding.

Management

- Tracheal obstruction, if it occurs, is an indication for emergency radiotherapy.
- Diuretics, head elevation and oxygen may provide temporary symptomatic relief in some patients.
- Radiotherapy (elective) is the treatment of choice for non-small-cell tumours of lung and metastatic tumours causing SVC syndrome.
- Chemotherapy is useful in some tumours like small-cell carcinoma of lung or lymphoma.
- If the patient is seriously ill (e,g, presence of hypotension, coma, stridor), empiric corticosteroids and cyclophosphamide may be given intravenously for temporary relief.
- Endovascular stent placement.
- Local, catheter-directed thrombolytic agents for SVC thrombosis.

Q. What are the common mediastinal masses? Discuss briefly the clinical features, investigations and management of mediastinal tumours.

Common Mediastinal Tumours, Cysts and Masses

Benign	Retrosternal goitre, thymoma, aortic aneurysm, neurogenic tumours, dermoid cysts, pericardial cysts, developmental cysts, lipoma
Malignant	Lymph node metastases (especially from bronchial carcinoma), lymphomas, leukaemias, malignant thymoma, mediastinal teratoma, seminoma, non-seminomatous germ-cell tumours

Common Mediastinal Lesions According to Location

Superior mediastinum	Thymoma, lymphoma, retrosternal goiter, aneurysm involving arch of aorta, thyroid malignancies,
Anterior mediastinum	Thymoma, very large retrosternal goiter, lymphoma, germ cell tumours
Middle mediastinum	Cysts (bronchogenic, oesophageal, pericardial), metastatic lymphadenopathy (from lung, oesophageal, and head and neck cancers), benign lymphadenopathy (tuberculosis, sarcoidosis, histoplasmosis, Castleman disease)
Posterior mediastinum	Neurogenic tumours, aneurysm of descending aorta

Clinical Features

- Germ cell tumours and lymphoma/leukaemias are more common between 20 and 40 years of age.
- Clinical features are due to the involvement of the structures of mediastinum. The mediastinal structures are involved by compression and/or invasion (infiltration). Benign tumours compress but do not invade, whereas malignant tumours compress and invade the vital structures of mediastinum.
- Clinical features resulting from the involvement of various structures of mediastinum are listed below:

Structure involved	Effects
• Oesophagus	Dysphagia
• Trachea and main bronchi	Stridor, dyspnoea, cough and lung collapse
• Phrenic nerve	Diaphragmatic paralysis and dyspnoea
• Left recurrent laryngeal nerve	Paralysis of left vocal cord resulting in hoarseness of voice and "bovine" cough
• Sympathetic trunk	Horner's syndrome
• SVC	SVC syndrome
• Pericardium	Pericarditis and/or pericardial effusion, cardiac tamponade

Investigations

- Sputum examination for malignant cells.
- Radiological studies:
  - Plain radiograph of chest can give certain clues. A benign tumour appears as a sharply circumscribed opacity situated mainly in the mediastinum but often encroaching on one or both lung fields. A malignant tumour has ill-defined margins and often presents as a generalised widening of the mediastinal shadow.
  - Fluoroscopic examination for paradoxical movement of the diaphragm, in diaphragmatic paralysis.
  - Barium swallow for oesophageal involvement.
- CT scan of thorax.
- Magnetic resonance imaging (MRI) is helpful for evaluating cystic lesions.
- Positron emission tomography (PET).
- α-foetoprotein and β-human chorionic gonadotropin levels in any male with an anterior or superior mediastinal mass (elevated in non-seminomatous tumours).
- Bronchoscopy in suspected cases of bronchial carcinoma.
- Mediastinoscopy is useful in removing lymph nodal tissue from anterior mediastinum.
- Exploratory thoracotomy for removal of part or all of the tumour for histopathological examination.

Management

- Benign mediastinal tumours should be removed surgically.
- SVC obstruction should be treated as outlined before (refer SVC syndrome).
- Lymph nodal metastases from bronchial carcinoma should be treated by radiotherapy and/or chemotherapy.
- Malignant thymoma is treated by radiotherapy.
- Treatments of lymphomas and leukaemias are discussed elsewhere.

Q. What are the types of pulmonary fibrosis?

Q. Enumerate the causes of interstitial fibrosis.

Q. Discuss the clinical features, radiological features and management of replacement fibrosis.

- A wide variety of pulmonary disorders heal by laying down fibrous tissue. This results in pulmonary fibrosis. There are two types of pulmonary fibrosis.

Replacement Fibrosis

- Fibrous tissue replaces the lung parenchyma damaged by suppuration or infarction.
- Common causes of replacement fibrosis include pulmonary tuberculosis, bronchiectasis, lung abscess, pulmonary infarcts and necrotizing pneumonias.
- The extent of fibrosis may vary from small nodular lesions (focal fibrosis) to extensive areas.
- Common causes of focal fibrosis include coal worker's pneumoconiosis (CWP), asbestosis and silicosis.

Interstitial Fibrosis

- This is diffuse fibrosis of lung parenchyma, which is the end result of interstitial lung diseases.
- Common causes of interstitial lung disease are listed below:
  - Connective tissue disorders
  - Radiation injury to lung
  - Cryptogenic fibrosing alveolitis
  - Extrinsic allergic alveolitis
  - Idiopathic pulmonary haemosiderosis
  - Drugs like nitrofurantoin, amiodarone, gold, bleomycin, busulphan and methotrexate.

Clinical Features of Replacement Fibrosis

- The most common cause of replacement fibrosis is pulmonary tuberculosis. Upper lobes are affected most frequently. Fibrosis is usually associated with bronchiectasis.
- History is characterised by cough with or without expectoration and dyspnoea. Sputum may be blood-tinged.

Physical Findings in the Chest

- Inspection and palpation reveals shift of the mediastinum towards the affected side (shift of trachea and apex beat), drooping of the shoulder, retraction and flattening of the chest (supraclavicular hollowing, infraclavicular flattening and suprascapular wasting), crowding of the ribs, diminished movements of the chest wall and scoliosis of the spine. On measurement, chest expansion is reduced, the affected hemithorax is smaller, the affected hemithorax expansion and spinoscapular distance are diminished. Vocal fremitus is variable and it may be increased or decreased (refer auscultation).
- Percussion note is impaired over the affected areas.

Auscultation

- In extensive fibrosis, the intensity of breath sounds is diminished and they are vesicular in character with prolonged expiration. Vocal resonance is diminished and coarse crepitations are heard.
- If a major bronchus or trachea lies subjacent to the fibrotic area (which is usually the situation because of the shift of trachea due to the pulling by fibrosis), the intensity of breath sounds is increased, breath sounds are low-pitched, bronchial in character, vocal resonance is increased and coarse crepitations are heard.

Radiological Findings

- Shift of the mediastinum towards the affected side
- Affected hemithorax is smaller than the other
- Crowding of the ribs
- Fibrous bands in the lung fields
- Hilum is pulled upwards
- Diaphragm is raised on the affected side (tenting)

Management of Replacement Fibrosis

- Symptomatic measures like expectorants, breathing exercises, etc.
- Treatment of intercurrent infections with antibiotics.
- Specific treatment of the underlying causes (e.g. tuberculosis).
- Supplemental oxygen in hypoxaemic patients.
- Resectional surgery or lung transplantation in selected cases.

Q. Discuss briefly about interstitial lung diseases.

Definition

- Interstitial lung diseases [also known as diffuse parenchymal lung diseases (DPLD)] are non-infectious and non-malignant, usually chronic conditions that diffusely involve the lungs but predominantly the interstitial tissue of the lungs. Pulmonary interstitium is the space between epithelial and endothelial basement membranes of the alveoli.
- These diseases often involve the alveoli, the capillary endothelium, as well as the perivascular and lymphatic tissues.
- Many of these can produce fibrosis in the interstitium (interstitial pulmonary fibrosis).

Aetiology

- A number of diseases can produce interstitial lung disease. Some of the common diseases are classified below:

ILD due to known causes	ILD due to unknown causes
Non-granulomatous interstitial inflammation	***Non-granulomatous interstitial inflammation***
• Drugs (antibiotics, gold, busulphan, bleomycin, methotrexate, D-penicillamine, nitrofurantoin, amiodarone)	• Idiopathic interstitial pneumonias (IIPs) (refer later)
	• Connective tissue diseases:
• Asbestos	• Systemic lupus erythematosus
	• Rheumatoid arthritis
• Fumes and gases	• Ankylosing spondylitis
• Radiation	• Systemic sclerosis
• Aspiration pneumonitis	• Sjogren's syndrome
• Residual of ARDS	• Diffuse pulmonary haemorrhage
• Toxins (e.g. paraquat)	• Goodpasture's syndrome
	• Idiopathic pulmonary haemosiderosis
	• Lymphocytic interstitial pneumonia (seen in HIV)
	• Pulmonary alveolar proteinosis
	• Eosinophilic pneumonias
	• Amyloidosis
	• Lymphangioleiomyomatosis (LAM)
	• Inherited disorders:
	• Neurofibromatosis
	• Tuberous sclerosis
	• Graft-versus-host disease

ILD due to known causes	ILD due to unknown causes
	• Gastrointestinal/liver diseases:
	• Chronic liver disease
	• Primary biliary cirrhosis
	• Ulcerative colitis
Granulomatous interstitial inflammation	*Granulomatous interstitial inflammation*
• Hypersensitivity pneumonitis	• Sarcoidosis
• Silicosis	• Pulmonary Langerhans cell histiocytosis
• Berylliosis	• Wegener's granulomatosis
	• Churg–Strauss syndrome

- Idiopathic pulmonary fibrosis (a type of idiopathic interstitial pneumonia), pulmonary fibrosis associated with connective tissue diseases and sarcoidosis are the most common types of ILDs.

Clinical Features

Acute Presentation

- Acute presentation is uncommon but can occur with drugs, acute idiopathic interstitial pneumonia and hypersensitivity pneumonitis.
- Patient presents with cough, dyspnoea and occasionally fever.
- Chest radiograph shows diffuse alveolar opacities and therefore can be confused with "atypical" pneumonia.

Subacute Presentation

- Patient presents with gradually increasing symptoms of cough and dyspnoea over weeks to months.
- This type of presentation can occur with all types of interstitial lung diseases especially sarcoidosis, drug-induced ILDs and SLE-associated ILD.

Chronic Presentation

- This is the most common presentation where the symptoms are present for months to years.
- Common symptoms are:
  - Shortness of breath, especially with exertion
  - Fatigue and weakness
  - Loss of appetite
  - Loss of weight
  - Dry cough
  - Chest pain and haemoptysis are unusual.
  - Sudden dyspnoea due to spontaneous pneumothorax can occur with lymphangioleiomyomatosis (LAM), pulmonary Langerhan's cell histiocytosis, tuberous sclerosis and neurofibromatosis.
  - Frank haemoptysis can occur with diffuse pulmonary haemorrhage, LAM and tuberous sclerosis.
  - Wheezing may occur with Churg–Strauss syndrome and sarcoidosis.

Examination

- Tachypnoea.
- Clubbing.
- Cyanosis.
- Bilateral superficial leathery crepitations (end-inspiratory).
- Features of right-sided heart failure in late stages.
- Signs of underlying aetiologies.

Investigations

Blood

- Blood investigations include total leucocyte count, ESR, urinalysis, renal and liver functions, antinuclear antibodies, rheumatoid factor and circulating immune complexes. The last three tests may be positive in some patients with idiopathic pulmonary fibrosis without underlying connective tissue disease.
- Serum precipitins in suspected hypersensitivity pneumonitis.
- Angiotensin converting enzyme levels are elevated in most patients with sarcoidosis.
- Antineutrophil cytoplasmic antibodies and anti-basement membrane antibodies if Wegener's granulomatosis and Goodpasture's syndrome, respectively are suspected.

Chest Radiography

- It often shows a bibasilar reticular or linear pattern.
- Mixed nodular pattern (of alveolar filling) along with reticular pattern.
- Nodular opacities (in some cases of sarcoidosis, chronic hypersensitivity pneumonitis, silicosis, rheumatoid arthritis).
- Ground glass appearance in early cases.
- Honeycombing (small 0.5–2.0 cm thick-walled cystic lesions) in long-standing conditions. These represent dilated and thickened terminal and respiratory bronchioles.
- Basal fibrosis with pleural thickening and pleural plaques suggest asbestosis.

Computed Tomography

- High-resolution CT of chest is superior to chest radiography for early detection and confirmation of suspected interstitial lung disease.
- It demonstrates the extent and distribution of disease.
- Shows co-existent pathology (e.g. lymph node involvement).

Pulmonary Function Tests

- Restrictive defect (reduced FVC, reduced FEV_1, normal or elevated FEV_1:FVC ratio, reduced total lung capacity and reduced diffusion capacity).
- Many ILDs are associated with an obstructive pattern in addition to restrictive pattern because of their bronchiolocentric propensity. These include sarcoidosis, hypersensitivity pneumonitis, LAM, tuberous sclerosis and neurofibromatosis.

Exercise Tests

- Exercise tests may help evaluation of disease severity. The six-minute walk test records oxygen saturation before, during, and after exercise and measures the total distance walked.

Arterial Blood Gas

- Hypoxaemia and respiratory alkalosis.
- Hypercapnia is rare until end-stage.
- Increased alveolar-arterial oxygen gradient [$PAO_2 - PaO_2$].

Bronchoscopy

- In some cases, analysis of BAL may be useful in narrowing down the possibilities among various types of interstitial lung diseases.
  - In sarcoidosis and hypersensitivity pneumonitis, BAL fluid shows T cell lymphocytosis (increased CD4 cells in sarcoidosis and CD8 cells in hypersensitivity pneumonitis).
  - In idiopathic pulmonary fibrosis (IPF), neutrophils and eosinophils predominate in BAL.
  - In pulmonary alveolar proteinosis, BAL is milky containing foamy macrophages and PAS-positive material.
  - In diffuse pulmonary haemorrhage, BAL shows red blood cells and haemosiderin-laden macrophages.
- Transbronchial biopsy may help in diagnosis.

Lung Biopsy (Open or Video Assisted)

- Confirmation of diagnosis.
- Assessment of activity.

Treatment

- Treatment of the underlying causes if possible.
- Removal of offending agent.

Drugs

- Corticosteroids are the mainstay of treatment though they are not effective in majority of the patients, particularly those with significant fibrosis. Dose is 1 mg/kg for 6–12 weeks, which is then tapered to a maintenance level if the patient improves.
- If the patient does not respond to steroids, another immunosuppressant (cyclophosphamide or azathioprine) is added.
- Other drugs include colchicine and cyclosporine.
- N-acetylcysteine is often combined with other medicines and has been found useful in some studies. It is a precursor to the naturally occurring antioxidant glutathione.
- Perfenidone, an anti-fibrotic agent due to its transforming growth factor-β inhibition properties, has been found to be useful in patients with idiopathic lung fibrosis.
- Antigastro-oesophageal reflux agents (as prevalence of gastro-oesophageal reflux is high in these patients).

Miscellaneous

- Oxygen therapy if PaO_2 <55 mmHg.
- Treatment of pulmonary hypertension and cor pulmonale.
- Lung transplant.
- Experimental therapies include interferon-γ1b, etanercept and infliximab (anti TNF-α), anticoagulants, bosentan (a dual endothelin-receptor antagonist) and imatinib mesylate.

Q. What are idiopathic interstitial pneumonias?

Q. Discuss the clinical features, investigations and treatment of idiopathic pulmonary fibrosis.

- Idiopathic interstitial pneumonias (IIPs) are a subset of acute and chronic lung disorders (collectively referred to as interstitial lung diseases or diffuse parenchymal lung diseases) which have no known aetiology. These disorders involve the lung parenchyma by varying combinations of fibrosis and inflammation.
- Based on clinicopathological criteria, these are further subdivided into eight types:
  - Usual interstitial pneumonia (UIP) or idiopathic pulmonary fibrosis (IPF).
  - Desquamative interstitial pneumonia (DIP).
  - Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD).
  - Acute interstitial pneumonia (AIP).
  - Cryptogenic organizing pneumonia (COP).
  - Non-specific interstitial pneumonia (NSIP).
  - Lymphoid interstitial pneumonia (LIP).
  - Idiopathic pleuroparenchymal fibroelastosis (IPPFE).
- AIP is an acute form (Hamman–Rich syndrome) which occurs in a small proportion of patients and is rapidly fatal.

Idiopathic Pulmonary Fibrosis

- Also known as UIP.
- Risk factors include smoking, exposure to antidepressants, chronic aspiration and exposure to toxic dust and fumes.

Clinical Features

- Middle-aged patients (generally 55–75 years); more common in males.
- Main features are progressive dyspnoea and dry cough which over years eventually lead to cyanosis, respiratory failure, pulmonary hypertension and cor pulmonale.
- The median survival is about 4 years.

- Examination reveals gross clubbing, cyanosis and bilateral superficial crepitations (end-inspiratory and velcro crepitations).
- Late features include peripheral oedema, pulmonary hypertension and cor pulmonale.
- Acute worsening of symptoms may occur due to infections, pulmonary embolism, pneumothorax or heart failure. Another reason for acute deterioration is acute exacerbation of IPF, characterised by worsening of dyspnoea within a few days to a month, new diffuse radiological opacities and absence of conditions listed above as the cause of acute worsening. HRCT shows new bilateral ground glass opacities and/or consolidation superimposed on a reticular pattern or honeycombing. Nearly 75% of patients with acute exacerbation of IPF die despite ventilatory support.

Investigations

- ESR is raised.
- Antinuclear antibodies and rheumatoid factor are present in nearly 30% of cases.
- Chest radiograph shows irregular reticulonodular shadows, more in the lower zones.
- High-resolution CT scan of the chest shows peripheral subpleural and basal reticular opacities with honeycomb appearance (typical UIP pattern; absence of honeycombing indicates possible UIP pattern). Ground glass appearance is uncommon.
- Pulmonary function tests show a restrictive pattern.
- Blood gas analysis shows hypoxaemia with normal or low CO_2.
- BAL shows increased number of cells, particularly neutrophils and macrophages. Lymphocytosis is not usual.
- Histological confirmation, if required, can be done by lung biopsy (transbronchial, video-assisted or open).

Diagnosis

Based on presence of the following criteria:

1. Exclusions of other possible causes of interstitial lung disease
2. Specific findings of usual interstitial pneumonia (UIP) on HRCT chest OR a combination of possible UIP findings on HRCT chest and UIP findings on lung biopsy

Treatment

- See "interstitial lung disease".
- Response to steroids is poor.

Q. Enumerate the common occupational lung diseases and give their aetiologies.

- Strictly speaking, the term 'pneumoconiosis' includes those occupational lung diseases which are due to exposure to inorganic or mineral dust that is retained in the lung parenchyma and incites fibrosis. In contrast, other occupational lung diseases which occur due to organic dust are not associated with such accumulation of particles within the lungs and are believed to have an immunologic pathogenesis. However, generally, both the terms are used interchangeably.

Aetiology	Diseases
• **Diseases due to mineral dusts**	
• Coal	Coal-worker's pneumoconiosis (CWP)
• Silica	Silicosis
• Asbestos	Asbestos-related diseases
• Iron oxide	Siderosis
• Tin dioxide	Stannosis
• Beryllium	Berylliosis

Aetiology	Diseases
• **Diseases due to organic dusts**	
• Cotton, flax or hemp dust	Byssinosis
• Mouldy hay, grain, silage	Farmer's lung
• Mouldy barley	Malt worker's lung
• Mushroom compost	Mushroom worker's lung
• Contaminated bagasse (sugar cane)	Bagassosis
• **Diseases due to gases and fumes**	
• Irritant gases, cadmium, isocyanates	Occupational asthma, bronchitis, ARDS
• Platinum salts	Occupational asthma
• **Diseases due to biological substances**	
• Proteolytic enzymes, animal and insect excreta, contaminated grain dust	Occupational asthma, bronchitis
• **Diseases due to chemicals and radioactive substances**	
• Polycyclic hydrocarbons, radon	Bronchial carcinoma

• Siderosis and stannosis are non-fibrotic forms of occupational lung diseases.

Q. What are the common pneumoconioses?

• Pneumoconioses are diseases caused by inhalation of mineral dusts.

Aetiology	Diseases
• Coal dust	Coal-worker's pneumoconiosis (CWP)
• Silica	Silicosis
• Asbestos	Asbestos-related diseases
• Iron oxide	Siderosis
• Tin dioxide	Stannosis
• Beryllium	Berylliosis

Q. Give a brief account of the asbestos-related diseases of lungs and pleura.

• The main types of asbestos are white asbestos (chrysotile), blue asbestos (crocidolite) and brown asbestos (amosite). All fibre types have the potential to cause asbestos-related diseases.
• Occupational exposure is highest with mining and milling of asbestos, manufacturing processes involving asbestos and demolition and shipyard workers. It can also occur in automobile and railroad workers and those involved in electrical wire insulation.
• There are six asbestos-related diseases:
  • Benign pleural plaques
  • Benign pleural effusion
  • Asbestosis (progressive pulmonary fibrosis)
  • Bronchial carcinoma
  • Mesothelioma of pleura
  • Mesothelioma of peritoneum (rare).
• Of all asbestos-related effects, highest dose is required to cause asbestosis.

Benign Pleural Plaques

• These are localised or diffuse areas of pleural thickening which are often calcified.
• Common sites are diaphragm and anterolateral pleural surfaces.
• Clinically, the patients are asymptomatic. The disease is usually identified on a routine chest radiograph.

- May lead to a significant decrease in total lung capacity, forced expiratory volume in 1 second and forced vital capacity (restrictive pattern)

Benign Pleural Effusion

- Benign (non-malignant) and self-limiting disease; may be bilateral.
- Associated with pleuritic pain, fever and leucocytosis.
- Pleural fluid is often haemorrhagic.
- Common complication is pleural fibrosis.
- Exclude pleural mesothelioma by thoracoscopy and biopsy.

Asbestosis

- Moderate to severe exposure for at least 10 years.
- Pathologically characterised by progressive pulmonary fibrosis.
- Clinically characterised by progressive exertional breathlessness, finger clubbing and end-inspiratory crepitations over lung bases.
- Radiologically (chest X-ray and HRCT) characterised by mottled shadows with some streaky opacities and sometimes "honeycombing" in the mid and lower zones. On plain chest radiograph, many do not manifest pleural disease; however, CT picks up pleural disease in more than 90% of cases.
- Pulmonary function tests show reduced carbon monoxide transfer factor, decreased lung volumes and a restrictive ventilatory defect.
- Lung biopsy may show asbestos bodies.
- Complications of asbestosis include respiratory failure, right ventricular failure and bronchial carcinoma.

Bronchial Carcinoma

- Either squamous cell carcinoma or adenocarcinoma.
- Minimum lapse of 15–20 years between exposure and development of carcinoma.
- Multiplicative effect of smoking (risk more than additive effect of smoking and asbestos).

Mesothelioma

- Mesothelioma is a primary malignant tumour of pleura, most commonly caused by blue asbestos.
- In contrast to bronchial carcinoma, development of mesothelioma is not related to smoking.
- Relatively short period of exposure (even 1–2 years) that occurred more than 20–30 years ago, is required.
- Clinically, the patient presents with chest pain, breathlessness and haemorrhagic pleural effusion.
- Although approximately 50% of mesotheliomas metastasise, the tumour is locally invasive and death usually occurs due to local invasion. On chest radiograph, the mediastinum is either not shifted or shifted to the same side (a point to differentiate from other effusions). Diagnosis is confirmed by closed pleural biopsy.

Q. Give a brief account of coal-worker's pneumoconiosis (CWP).

Q. What is progressive massive fibrosis (PMF)?

Q. Write a short note on Caplan's syndrome (rheumatoid pneumoconiosis).

- Coal-worker's pneumoconiosis (CWP) is seen in coal miners with a prolonged history of inhalation of coal dust. More common in anthracite coal miners as compared to bituminous miners.
- Chronic obstructive pulmonary disease is often associated with CWP.
- CWP is subdivided into two:
  1. Simple CWP
  2. Progressive massive fibrosis (PMF)

Simple Coal-Worker's Pneumoconiosis

- Develops after prolonged exposure (15–20 years) to coal dust.
- Does not progress if the miner leaves the industry.
- There is considerable dispute whether simple CWP can produce significant symptoms though many patients have cough and dyspnoea.

- Depending on the site and extent of the nodulation, simple CWP is radiologically divided into three categories:
  1. Category 1: Few small round opacities.
  2. Category 2: Numerous small round opacities but normal lung markings still visible.
  3. Category 3: Numerous small round opacities and the normal lung markings partly or fully obscured.
- The importance of simple CWP is that categories 2 and 3 can advance to PMF.

Progressive Massive Fibrosis (PMF)

- This condition progresses even after the miner leaves the industry.
- Characterised by single or multiple nodules (>1 cm in size to large dense masses in the upper lobes, which may cavitate).
- Clinically characterised by cough with blackish expectoration (melanoptysis) and progressive breathlessness.
- Complications of PMF include pulmonary tuberculosis, respiratory failure, right ventricular failure and Caplan's syndrome.

Caplan's Syndrome

- Caplan's syndrome is PMF co-existing with sero positive rheumatoid arthritis.
- Rounded fibrotic nodules of 0.5–5 cm diameter are seen mainly in the periphery of the lung fields.
- Rheumatoid factor is positive.
- This syndrome is also seen in a number of pneumoconioses (e.g. silicosis) other than CWP.

Q. Give a brief account of silicosis.

- Silicosis is caused by inhalation of silica dust or quartz particles.
- Occupations with high risk include mining, quarrying, dressing of sandstone and granite, pottery and ceramics industry, boiler scaling, sandblasting, etc. Silica is highly fibrogenic and causes development of hard nodules that coalesce as the disease advances.
- Tuberculosis commonly complicates silicosis (silicotuberculosis). The increased risk of both pulmonary and EPTB is lifelong even if exposure ceases. Chemoprophylaxis using INH for 9 months is recommended if latent tuberculosis is diagnosed with a positive tuberculin test.
- Silica exposure increases the risk for developing lung cancer, chronic renal insufficiency and autoimmune diseases, particularly scleroderma, rheumatoid arthritis and Wegener's granulomatosis. It can also produce chronic airway obstruction similar to COPD.
- Silicosis (silica-induced lung disease) can present in three forms: chronic, acute or accelerated.

Chronic or Simple Silicosis

- It is the most common form of silicosis which occurs after many decades of exposure to relatively low levels of silica.
- This form of silicosis is characterised by gradually progressive dyspnoea and dry cough. It is often compatible with normal life.
- The radiological features of silicosis are variable and range from diffuse fine rounded regular nodulation resembling miliary tuberculosis through coarse irregular nodules to extensive fibrosis resembling PMF. In early stages, upper zones of the lungs are more commonly involved as compared to the lower zones. The involvement of lymph nodes by chronic silicosis is fairly characteristic, with a tendency towards peripheral calcification, which produces the so-called egg shell appearance. Other causes of lymphnode calcification include sarcoidosis, radiation-treated Hodgkin's disease, sclero-derma and histoplasmosis.
- Pulmonary function tests typically reveal a mixed pattern of obstruction and restriction with a reduced diffusion capacity.
- May lead to PMF.
- No specific treatment available.

Acute Silicosis

- It occurs after exposure to a very high concentration of dust over a few months and is usually rapidly fatal within years.
- Characterised by pulmonary oedema, interstitial inflammation and accumulation of proteinaceous fluid rich in surfac-tant within the alveoli.

- Chest radiograph may show military infiltration or areas of consolidation. HRCT chest may show a characteristic "crazy paving" pattern.
- Whole lung lavage via multiple bronchoscopies may slow progression.

Accelerated Silicosis

- It occurs after a few years of exposure to silica and is associated with rapidly progressive features of dyspnoea and pulmonary fibrosis. Involvement of middle and lower zones of the lungs is more frequent as compared to chronic silicosis.

Q. Discuss the clinical features, investigations and management of sarcoidosis.

Q. Describe Lofgren's syndrome.

Q. Give a brief account of Heerfordt–Waldenstrom syndrome.

Definition

- Sarcoidosis is a multisystem, chronic granulomatous inflammatory disorder of unknown aetiology. It is characterised by the accumulation of T lymphocytes and mononuclear phagocytes and non-caseating epithelioid granulomas in the affected organs.

Aetiology

- Aetiology of sarcoidosis is unknown.
- The disease probably results from an exaggerated cellular immune response to an infectious or non-infectious environmental agent in a person genetically susceptible to develop sarcoidosis. Probable infectious agents include *Propionibacterium acnes*, atypical mycobacteria and a *M. tuberculosis protein*. Non-infectious agents include insecticides and molds.

Pathology

- Sarcoidosis can affect any part of the body. The most frequently involved organ is lung. The other organs commonly involved are lymph nodes, eyes, skin, parotid glands, liver, spleen and kidneys.
- The characteristic histologic feature of sarcoidosis is non-caseating epithelioid granulomas. Tuberculosis, on the other hand, is characterised by caseating epithelioid granulomas with tubercle bacilli.

Clinical Features

- Sarcoidosis can manifest in three forms:
  1. Asymptomatic form (30–45%).
  2. Acute or subacute form (10–15%).
  3. Chronic form (40–60%).
- Asymptomatic form is usually detected incidentally on a routine chest film.
- Acute or subacute form develops abruptly over a period of few weeks. Patients have constitutional symptoms like fever, fatigue, malaise, anorexia and weight loss. Respiratory symptoms are cough, dyspnoea and retrosternal chest discomfort. Two syndromes have been identified in the acute group:
  1. Lofgren's syndrome characterised by fever, erythema nodosum, joint symptoms and radiographic evidence of bilateral hilar adenopathy. Uveitis may occur in some patients. It resolves over 6 months–2 years with NSAIDs.
  2. Heerfordt–Waldenstrom syndrome or uveoparotid fever characterised by anterior uveitis, parotid enlargement, fever and facial palsy.
- Chronic form develops over months, characterised by respiratory complaints without significant constitutional symptoms. Clubbing and haemoptysis are uncommon. The disease keeps waxing and waning over many years with nearly 60% recovering spontaneously over 10 years. Pulmonary hypertension may occur due to pulmonary fibrosis; other causes include granulomatous infiltration of the pulmonary arteries and direct compression by lymphadenopathy. Patients with chronic form of sarcoidosis have increased risk of developing lymphoproliferative disorders (Hodgkin and non-Hodgkin lymphomas).

Pulmonary Manifestations
- Interstitial lung disease.
- Atelectasis.
- Cavitation.
- Unilateral pleural effusion.
- Pulmonary nodules.

Extrapulmonary Manifestations

• Lymph nodes	Hilar adenopathy (70–90%), paratracheal and generalised lymphadenopathy
• Skin	Erythema nodosum, plaques, maculopapular eruptions, subcutaneous nodules, lupus pernio, keloid, infiltration of previous scars and tattoos by granuloma
• Eyes	Uveitis, iridocyclitis, retinitis, phlyctenular conjunctivitis, lacrimal gland involvement (dry eyes)
• Salivary glands	Parotid gland enlargement
• Heart	Myocarditis, pericarditis, papillary muscle dysfunction, CHF, conduction defects, arrhythmias
• Liver and spleen	Hepatosplenomegaly, hypersplenism, portal hypertension
• Nervous system	Seventh nerve, cerebral, meningeal and peripheral nerve involvement, optic neuritis, diabetes insipidus due to hypothalamic involvement
• Kidneys	Nephrocalcinosis, nephrolithiasis, tubuloglomerula and renal artery disease
• Musculoskeletal	Arthralgias, arthritis, phalangeal cysts, polymyositis, chronic myopathy
• Endocrine	Diabetes insipidus, anterior pituitary dysfunction, Addison's syndrome

Lupus Pernio
- Skin lesions around nose, eye and cheeks.
- These lesions are often disfiguring and can erode into cartilage and bone, especially around the nose.
- Associated with poor prognosis of sarcoidosis and is associated with more severe pulmonary disease.

Investigations
- Blood examination shows lymphocytopenia, anaemia, eosinophilia, raised ESR, hyperglobulinaemia and elevated serum alkaline phosphatase.
- Hypercalcaemia and hypercalciuria occur uncommonly (occur due to increased production of 1,25-dihydroxyvitamin D by the granuloma).
- Plasma level of angiotensin-converting enzyme (ACE) is elevated in about 70% of cases with acute disease and only 20% of with chronic disease. It may also be elevated in several other diseases including tuberculosis, leprosy and hyperthyroidism. In lymphoma, ACE level is usually lower than normal range.
- Skin sensitivity to tuberculin is depressed or absent because activated T cells are sequestered in the lung, leading to peripheral depletion. So, Mantoux test is a useful screening test. A strongly positive reaction virtually rules out sarcoidosis.
- Kveim (or Kveim–Siltzbach) test involves the intradermal injection of 0.1 mL of an antigen obtained from sarcoidosis spleen extract. If the test is positive, a small nodule develops at the injection site. The nodule is biopsied at 4–6 weeks. It shows typical sarcoid lesions (non-caseating epithelioid granulomas). However, the test is obsolete now.

Radiological Features of Sarcoidosis

• Hilar adenopathy, usually bilateral (70–90%)	• Large nodules
• Reticulo-nodular shadows in lung fields (usually upper lobes)	• Cavitation
• Paratracheal lymph nodal enlargement	• Atelectasis
• Egg shell calcification of hilar nodes (unusual)	• Cardiomegaly
• Pleural effusion (very uncommon)	

- In addition to sarcoidosis, upper lobe involvement occurs with tuberculosis, *Pneumocystis* pneumonia, hypersensitivity pneumonitis, silicosis and Langerhans cell histiocytosis.

Classic Radiographic Patterns of Pulmonary Sarcoidosis

• Stage I	Bilateral hilar adenopathy with no parenchymal abnormalities (50% cases)
• Stage II	Bilateral hilar adenopathy with diffuse parenchymal infiltrates (30% cases)
• Stage III	Diffuse parenchymal infiltrates without hilar adenopathy (10% cases)
• Stage IV	Evidence of diffuse pulmonary fibrosis

- Computed tomography of the chest (contrast-enhanced) is helpful in better delineation of the hilar and mediastinal lymph nodes. These lymph nodes are homogeneous and do not show any evidence of necrosis or rim enhancement (features typically seen in tubercular involvement of mediastinal nodes).
  - HRCT shows reticular shadows and nodules. Confluence of numerous interstitial granulomas can result in large, irregular, mass-like opacities (alveolar sarcoid). Small satellite nodules are often present at the periphery of these large nodules, termed the "galaxy sign" (a collection of stars). Honeycombing is uncommon.
  - Airway involvement results in nodular bronchial wall thickening, small endobronchial lesions and obstructive small airways disease. Bronchi can be seen to be obstructed by either endobronchial granulomas or extrinsic compression by enlarged lymph nodes, leading to atelectasis, particularly of the right middle lobe.
  - A rare variant is necrotising sarcoid granulomatosis that is generally asymptomatic and may only be detected incidentally by chest imaging. The findings include multiple, bilateral, often confluent lung nodules usually without enlarged hilar and mediastinal lymph nodes. Diagnosis is confirmed by lung biopsy. Response to corticosteroid is good.
- The pulmonary functions tests reveal a typical restrictive pattern. Occasionally, obstructive pattern may be seen.
- The gallium-67 scan shows diffuse uptake. However, it may become negative within a few days of start of corticosteroids.
- PET scan using radiolabeled fluorodeoxyglucose is more useful than gallium-67 scan to detect both pulmonary and extra-pulmonary sites with active inflammation, thereby indicating possible sites of biopsy.
- Bone marrow examination may show granulomas in about 30% cases.
- BAL shows increased proportion of lymphocytes, most of which are activated Th1 (subset of CD4+ cells) cells.
- Transbronchial biopsy may show non-caseating granulomas with epithelioid cells and multinucleated giant cells.
- Mediastinoscopic biopsy of mediastinal or hilar lymph nodes.
- MRI may be useful in brain and cardiac involvement.

Causes of Pulmonary Granulomas

Infectious diseases	Non-infectious diseases

• Mycobacterial infections:
  • *Mycobacterium tuberculosis*
  • Nontuberculous mycobacteria (NTM)
• Fungal infections:
  • *Histoplasma*
  • *Cryptococcus*
  • *Coccidioides*
  • *Blastomyces*
  • *Pneumocystis*
  • *Aspergillus*
• Others infections:
  • Brucella
  • Chalamydia
	• Sarcoidosis
	• Lymphoma
	• Chronic beryllium disease
	• Hypersensitivity pneumonitis
	• Wegener's granulomatosis
	• Churg–Strauss syndrome
	• Talc granulomatosis
	• Rheumatoid nodule

Treatment

- Sarcoidosis is divided into four stages based on chest radiograph and clinical manifestations.
- Stage I disease usually resolves spontaneously and does not require treatment unless patient is significantly symptomatic.
- Symptomatic or progressive stages II and III of pulmonary disease and sarcoidosis involving vital structures are treated with corticosteroids. Prednisolone is given 20–40 mg daily for 4 weeks, followed by a maintenance dose of 7.5–10 mg daily for 6–18 months.
- Azathioprine and methotrexate as steroid-sparing agents that are given if patient cannot be maintained on prednisolone dose of 10 mg/day or less.
- Hydroxychloroquine is for skin, bone and joint involvement.
- Other agents used include mycophenolate, infliximab, etanercept (less effective than infliximab) and thalidomide.

Poor Prognostic Factors

- Age at onset >40 years
- Presence of hypercalcaemia
- Extrathoracic disease
- Lupus pernio
- Splenomegaly
- Pulmonary infiltrates on chest radiographs
- Chronic uveitis
- Cystic bone lesions

Q. Discuss the causes, clinical features, investigations and management of pleural effusion.

Q. How will you differentiate transudative pleural effusions from exudative pleural effusions?

Q. Describe Phantom tumour.

Q. What is Grocco's sign?

Definition

- Abnormal accumulation of fluid between parietal pleura and visceral pleura is called pleural effusion. Accumulation of purulent fluid is called empyema. Normally, the pleural space contains a small amount of fluid (about 0.26 ± 0.1 mL/kg) which allows the lungs to inflate and deflate with minimal friction.
- A minimum of 500 mL of fluid is necessary for clinical detection of pleural effusion.
- Transudate is an ultrafiltrate of plasma, resulting from increased hydrostatic pressure or decreased serum oncotic pressure. This is essentially an effusion with normal pleura. Transudative effusions are also called hydrothorax although some use this term for any pleural effusion.
- Exudate resembles plasma and is rich in proteins. This results from increased capillary permeability. This is essentially an effusion with diseased pleura.

Classification and Causes

•	Transudates	Congestive heart failure, cirrhosis of liver, nephrotic syndrome, severe malnutrition, peritoneal dialysis, hypothyroidism, constrictive pericarditis, Meigs' syndrome (benign ovarian tumours with ascites and pleural effusion)
•	Exudates	Tuberculosis, malignancy, pneumonia, pulmonary infarction, rheumatoid arthritis, pancreatitis, systemic lupus erythematosus, drug-induced effusion, benign asbestos-related effusion, Dressler's syndrome, intra-abdominal abscess, Meigs' syndrome (can be transudative as well), ruptured amoebic liver abscess, chylous pleural effusion

Clinical Features

- Symptoms and signs of pleurisy may precede the development of pleural effusion.
- Breathlessness may occur, the severity of which is related to the size and rate of accumulation of fluid.

Physical Findings in the Chest

- Inspection and palpation will disclose shift of trachea and mediastinum (shift of apex beat) to the opposite side, reduction in the chest movements on the affected side, bulging of the intercostal spaces, fullness of the affected chest and markedly reduced vocal fremitus. Measurements reveal diminished chest expansion, increase in the size of the affected hemithorax and an increase in spinoscapular distance.
- Percussion reveals a stony dull note over the fluid. Upper level of the dullness is highest laterally in the axilla, and is lower anteriorly and posteriorly (Ellis-S-shaped curve). A small pleural effusion on the left side may be detectable only by the obliteration of Traube's space on percussion. Likewise, a small effusion on the right side may be detectable only by tidal percussion.
- On auscultation, intensity of the breath sounds is markedly diminished-to-absent over the fluid. Adventitious sounds are not audible. Vocal resonance is markedly diminished over the fluid. Occasionally, aegophony, whispering pectoriloquy and a tubular bronchial breathing may be audible just above the level of a pleural effusion.

Grocco's Sign (Grocco's Triangle; Paravertebral Triangle of Dullness)

- In moderate- to large-sized pleural effusions, a triangular area of dullness or impaired note can be percussed over the back of chest on the contralateral side or opposite side of the effusion. This is probably due to shift of the posterior mediastinum to the opposite side by effusion.
- The Grocco's triangle is bounded medially by the midspinal line from the upper level of effusion down to the level of the tenth thoracic vertebra. It is bounded below by a horizontal line of about 3–7 cm extending laterally from the tenth thoracic vertebra, along the lower limit of lung resonance. It is bounded laterally by a curved line connecting the above two lines.

Investigations

Chest Radiograph

- Chest radiograph (posteroanterior view) in the erect posture can detect pleural effusion. A minimum of 200 mL of fluid is required for detection in this view.
- Chest radiograph (anteroposterior view) in the supine posture needs even larger amounts for detection. Here, the fluid layers are out posteriorly and gives a generally hazy shadow (ground glass appearance) with preserved vascular shadows. This is the usual radiological appearance in bedridden patients.
- Chest radiograph (lateral decubitus view) with the affected side down can detect an effusion as small as 100–150 mL. However, only 50 ml of pleural fluid can produce detectable posterior costophrenic angle blunting on a lateral chest X-ray.
- Loculated effusions are typically seen in conditions which cause intense pleural inflammation (e.g. tuberculosis, parapneumonic effusion, empyema and haemothorax).However, even malignancy, pulmonary embolism and congestive heart failure may also produce loculated effusion.
- In heart failure, loculated fluid within lung fissure may give the appearance of an intraparenchymal mass which disappears with diuretic therapy (phantom tumour or vanishing tumour).

Radiological Features of Pleural Effusion in an Erect Chest Film

- Mediastinal shift to the opposite side
- Obliteration of costophrenic angle
- A dense uniform opacity in the lower and lateral part of hemithorax
- Upper border of the opacity is concave upwards and is highest laterally
- Wider than normal interlobar fissure in "interlobar effusion"
- Encysted interlobar effusion may be seen as a rounded opacity resembling solitary pulmonary nodule (phantom tumour)
- Encysted effusion in the presence of adhesions between contiguous pleural surfaces (loculated effusion)
- Shift of mediastinum towards the side of effusion in a patient with massive effusion indicates either an endobronchial obstruction or a mediastinum encasement by tumour (e.g. mesothelioma)

Ultrasonography

- Can detect as little as 5 mL of effusion.
- It is useful in differentiating loculated pleural effusion from pleural tumour or pleural thickening.

- It detects septations within pleural fluid with greater sensitivity than CT scanning.
- Useful in localisation of an effusion prior to aspiration and biopsy.
- Detection of solid pleural abnormalities may suggest pleural malignancy.

Pleural Aspiration and Fluid Analysis

- At diagnostic aspiration, at least 50 mL of pleural fluid should be withdrawn. The fluid is collected in separate containers for microbiological examination including culture for mycobacteria, cytological examination including malignant cells and biochemical examination.
- Aspiration should not be performed for bilateral effusions in a clinical setting strongly suggestive of a transudate unless there are atypical features or they fail to respond to therapy.
- Exudative fluid can be differentiated from transudative fluid as per the table given below.

Pleural Fluid Analysis

Test	Transudate	Exudate
• Appearance	Clear	Clear, cloudy or haemorrhagic
• Protein		
• Absolute value	<3.0 g/dL	>3.0 g/dL
• Pleural fluid:serum ratio	<0.5	>0.5
• Lactic dehydrogenase		
• Absolute value	<200 IU/L	>200 IU/L
• Pleural fluid:serum ratio	<0.6	>0.6
• Glucose	>60 mg/dL (usually same as in blood)	<60 mg/dL (variable)
• Leucocytes		
• Total leucocytes	<1000/mm^3	>1000/mm^3
• Differential leucocytes	>50% lymphocytes or mononuclear cells	>50% lymphocytes (tuberculosis, malignancy) >50% polymorphs (acute inflammation)
• Erythrocytes	<500/mm^3	Variable

Note

- A low pleural fluid glucose concentration (<60 mg/dL) suggests complicated parapneumonic effusion, empyema, malignancy or tuberculosis. Very low levels (<15 mg/dL) are characteristic of rheumatoid effusions.
- Pleural fluid eosinophilia (>10% of all cells) may be seen in resolving infections, hydropneumothorax and asbestos-related pleural effusion.
- Pleural fluid erythrocyte counts exceeding 100,000/mm^3 are most often seen in malignancy and pulmonary embolism.
- Pleural fluid pH is a very unreliable guide to differentiate between transudates and exudates. However, a pleural fluid pH below 7.2 in a patient with a parapneumonic effusion indicates the need for drainage of the fluid.
- Pleural fluid amylase is elevated in patients with malignancies, pancreatic diseases and oesophageal rupture. However, routine amylase estimation is not recommended unless the clinical features suggest either of the two diseases.
- Pleural fluid triglycerides help in diagnosis of chylothorax
- Pleural fluid determination of antinuclear antibody titres or rheumatoid factor levels adds little diagnostic information and is not indicated in most cases.
- Other special characteristics of pleural fluid in relation to various diseases are discussed along with individual diseases (ADA estimation discussed under "tuberculous pleural effusion").

Light's Criteria

- Light's criteria are used to differentiate exudative from transudative fluid. These include one or more of the following:

- Ratio of pleural fluid protein to serum protein level >0.5
- Ratio of pleural fluid LDH to serum LDH >0.6
- Pleural fluid LDH level >2/3rd of the upper level of serum LDH levels

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- These criteria are highly sensitive for identifying exudative fluid but have lower specificity, i.e. some patients with transudative effusion will be classified as exudative fluid using this criteria. Therefore, if clinical findings suggest a transudative effusion but the pleural fluid appears to be an exudate on Light's criteria, the difference between the albumin level in serum and pleural fluid should be measured. Almost all patients with transudative effusion have a serum albumin level that is more than 1.2 g/dL higher than the pleural fluid albumin level (serum-effusion albumin gradient).
- Of note, a large percentage of exudates will be misclassified if serum-effusion albumin gradient is used as the only method of differentiating between transudates and exudates.

Causes of Lymphocytic Pleural Effusions

- Malignancy (primary or secondary)
- Tuberculosis
- Lymphoma
- Congestive heart failure (long standing)
- Rheumatoid effusion
- Chylothorax
- Uraemic pleuritis

Pleural Biopsy

- Usually indicated in some exudates that are undiagnosed.
- Closed pleural biopsy can be performed with Abrams or Cope or Tru-cut needle. It should be done under ultrasound guidance when the effusion is small or loculated.
- The needle should be inserted through an intercostal space at the area of maximum dullness on percussion and at the site of maximum radiological opacity or at a site determined by ultrasonography.

Other Investigations in Pleural Effusion

- Pleural fluid tumour markers like carcinoembryonic antigen (CEA), cancer antigen 125 (CA-125), cancer antigen 15–3 (CA 15–3) and cytokeratin 19 fragments (CYFRA) do not have any role in routine investigations of pleural effusion. However, immunocytochemical markers (e.g. epithelial membrane antigen, CEA, calretinin, etc.) can be performed on the atypical cells seen in the effusion.
- Blood examination for total and differential leucocyte counts, ESR, proteins, sugar, LDH, amylase, rheumatoid factor and antinuclear factor.
- Sputum examination for tubercle bacilli and malignant cells.
- Mantoux test.
- In a massive effusion, a repeat radiograph after removal of a large volume of fluid may reveal an underlying parenchymal lesion.
- CT scan of chest.
- Biopsy or fine needle aspiration of scalene lymph nodes.
- Bronchoscopy and biopsy.
- Thoracoscopy (video-assisted or open surgical) and biopsy.

Management of Pleural Effusion

- Treatment of the underlying causes.
- Therapeutic aspiration may be necessary to relieve dyspnoea. Not more than 1 L should be removed at a sitting because pulmonary oedema (refer below) may follow removal of large volumes.
- Insertion of chest tube if rapid reaccumulation of fluid occurs.
- Pleurodesis for malignant effusion using bleomycin or talc powder.

Evaluation of a Patient with Pleural Effusion
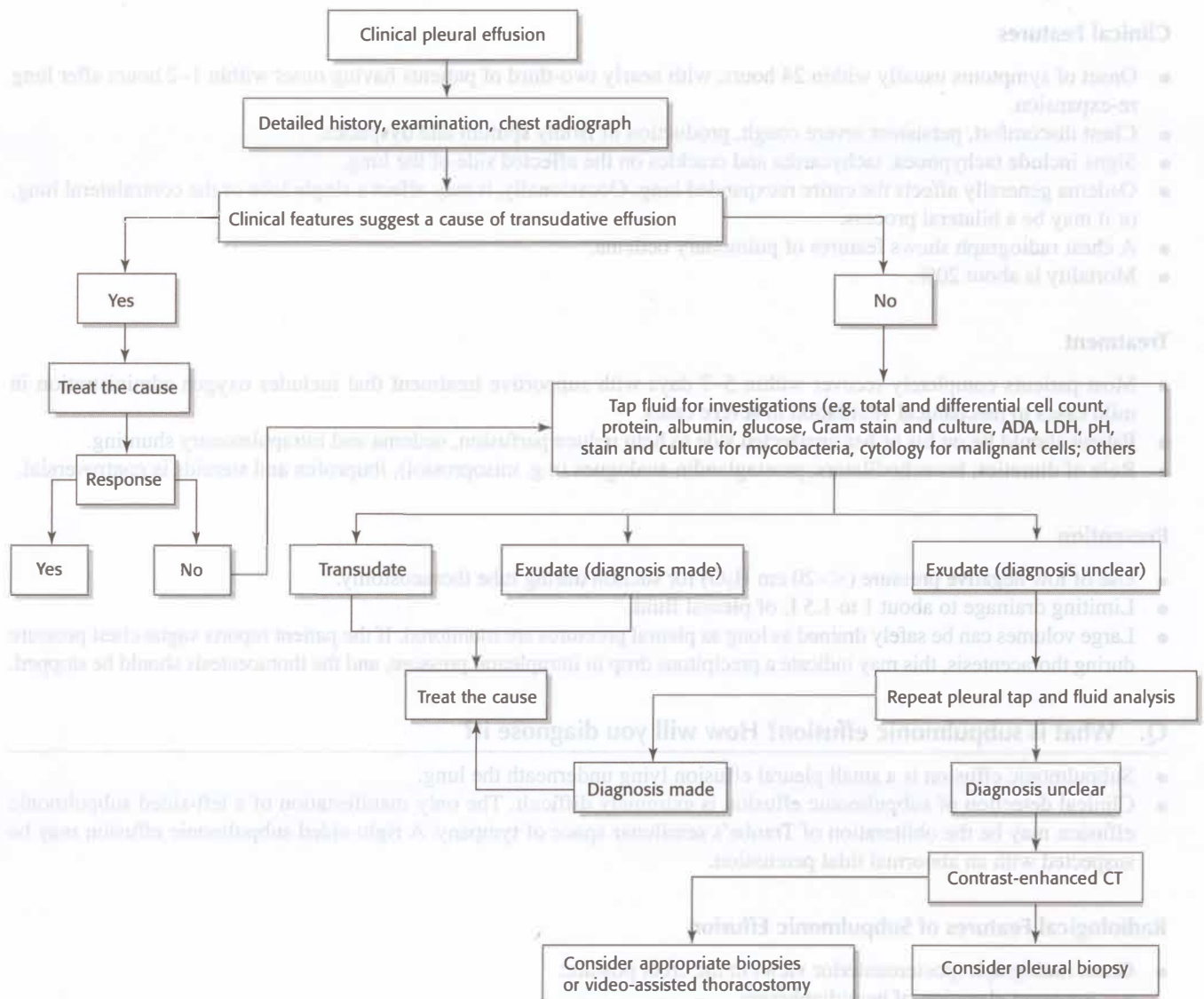
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                          ┌─────────────────────────────┐
                          │   Clinical pleural effusion  │
                          └──────────────┬──────────────┘
                                         │
                ┌────────────────────────┴────────────────────────┐
                │ Detailed history, examination, chest radiograph  │
                └────────────────────────┬────────────────────────┘
                                         │
            ┌────────────────────────────┴────────────────────────────┐
            │ Clinical features suggest a cause of transudative effusion│
            └─────────┬──────────────────────────────────────┬────────┘
                      │                                        │
                 ┌────┴────┐                              ┌────┴────┐
                 │   Yes   │                              │   No    │
                 └────┬────┘                              └────┬────┘
                      │                                        │
            ┌─────────┴─────────┐                              │
            │  Treat the cause  │                              │
            └─────────┬─────────┘                              │
                      │                                        │
                 ┌────┴─────┐        ┌──────────────────────────────────────────────────────┐
                 │ Response │        │ Tap fluid for investigations (e.g. total and          │
                 └────┬─────┘        │ differential cell count, protein, albumin, glucose,   │
                      │              │ Gram stain and culture, ADA, LDH, pH, stain and       │
            ┌─────────┴─────────┐    │ culture for mycobacteria, cytology for malignant      │
            │                   │    │ cells; others                                         │
        ┌───┴───┐          ┌───┴───┐ └──────────────────────────────────────────────────────┘
        │  Yes  │          │  No   │
        └───────┘          └───────┘
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Pathogenesis

- Exact reason for development of reexpansion of pulmonary oedema is not known.
  - Ventilation and reperfusion of a previously collapsed lung may lead to an inflammatory response, with production of reactive oxygen species and superoxide radicals, which results in increased capillary permeability.
  - Increased pulmonary hydrostatic pressure caused by enhanced venous return.
  - Pressure-induced mechanical disruption of alveolar capillaries.
  - Decreased levels of functional surfactant.
  - Increased pressure across the capillary-alveolar membrane from bronchial obstruction.
  - Altered lymphatic clearance.

Clinical Features

- Onset of symptoms usually within 24 hours, with nearly two-third of patients having onset within 1–2 hours after lung re-expansion.
- Chest discomfort, persistent severe cough, production of frothy sputum and dyspnoea.
- Signs include tachypnoea, tachycardia and crackles on the affected side of the lung.
- Oedema generally affects the entire reexpanded lung. Occasionally, it may affect a single lobe or the contralateral lung, or it may be a bilateral process.
- A chest radiograph shows features of pulmonary oedema.
- Mortality is about 20%.

Treatment

- Most patients completely recover within 5–7 days with supportive treatment that includes oxygen administration in mild cases to mechanical ventilation in severe cases.
- Patient should lie on his or her unaffected side to help reduce perfusion, oedema and intrapulmonary shunting.
- Role of diuretics, bronchodilators, prostaglandin analogues (e.g. misoprostol), ibuprofen and steroids is controversial.

Prevention

- Use of low negative pressure (<-20 cm H_2O) for suction during tube thoracostomy.
- Limiting drainage to about 1 to 1.5 L of pleural fluid.
- Large volumes can be safely drained as long as pleural pressures are monitored. If the patient reports vague chest pressure during thoracentesis, this may indicate a precipitous drop in intrapleural pressure, and the thoracentesis should be stopped.

Q. What is subpulmonic effusion? How will you diagnose it?

- Subpulmonic effusion is a small pleural effusion lying underneath the lung.
- Clinical detection of subpulmonic effusion is extremely difficult. The only manifestation of a left-sided subpulmonic effusion may be the obliteration of Traube's semilunar space of tympany. A right-sided subpulmonic effusion may be suspected with an abnormal tidal percussion.

Radiological Features of Subpulmonic Effusion

- Chest radiograph (posteroanterior view) in the erect posture:
  - Apparent elevation of hemidiaphragm.
  - Lateral displacement and slight flattening of the apparent dome of the diaphragm.
  - A wide density between the gastric air bubble and apparent upper border of the diaphragm (in left-sided subpulmonic effusion).
- Chest radiograph (lateral decubitus view) with the affected side down will show the pleural fluid layering out along the lateral chest wall.
- Ultrasonographic examination can detect a subpulmonic effusion with more certainty.

Q. What are the common causes of haemorrhagic pleural effusion? Give a brief account of malignant pleural effusion.

Causes of Haemorrhagic Pleural Effusion

- Malignancy
- Pulmonary infarction
- Benign asbestos-related pleural effusion
- Tuberculosis (uncommonly)
- Post-cardiac injury effusion

Differentiation Between Haemorrhagic Effusion and Haemothorax

- A haemothorax can be distinguished from haemorrhagic pleural effusions by performing a haematocrit on the pleural fluid. A pleural fluid haematocrit >50% of the patient's peripheral blood haematocrit is diagnostic of a haemothorax.

Malignant Pleural Effusion

- Malignant effusions are due to either a primary malignancy of pleura (e.g. mesothelioma) or secondary invasion of pleura from a primary malignancy elsewhere in the body (more commonly). Most malignancy-associated effusions occur with lung cancers (35%), breast cancers (25%) and lymphomas (10%).
- The effusion is usually due to the local effects of the tumour, like lymphatic obstruction or bronchial obstruction with pneumonia or atelectasis. It can also be a result of systemic effects of the tumour elsewhere.
- The effusion is usually unilateral, massive and often symptomatic.

Causes of Dyspnoea in Patients with Malignancy

- Pleural effusion
- Lymphangitis carcinomatosis
- Airway obstruction
- Radiation pneumonitis
- Chest wall invasion
- Direct effects of a tumour mass on the lung
- Underlying lung disease
- Pulmonary vascular disease (e.g. pulmonary emboli)
- Cardiac compromise
- Pericardial disease

- The characteristic feature of a malignant pleural effusion is rapid reaccumulation of fluid after aspiration.
- The pleural fluid is often haemorrhagic, with a high erythrocyte count (>100,000/mm^3). It shows the characteristics of an exudate, like high protein content (>3.0 g/dL), high LDH levels (>200 IU/L), low glucose levels (<60 mg/dL) and a total leucocyte count exceeding 1000/mm^3. The predominant cells in the pleural fluid are lymphocytes (>50%). Clumps of malignant cells may be seen in the pleural fluid on cytological examination.
- Closed pleural biopsy can demonstrate malignancy in about 40% of the cases.

Treatment

- Asymptomatic effusions do not require any treatment.
- Mildly symptomatic cases are treated by repeated aspirations.

- Severely symptomatic and recurrent effusions are treated by pleurodesis. This involves instillation of tetracycline hydrochloride, talcum powder, bleomycin or inactivated *Corynebacterium parvum* into the pleural cavity. This induces an intense inflammatory reaction in the pleura, followed by extensive pleural adhesions. Talc is more effective than other agents.
- Alternatively, thoracotomy with pleurectomy or pleural abrasion may be tried.

Q. Describe parapneumonic effusion (synpneumonic effusion and post-pneumonic effusion).

- Parapneumonic effusion is a pleural effusion complicating pneumonia or lung abscess.
  - It is more frequent with bacterial pneumonias, especially Gram-negative and pneumococcal. Here, the effusion is large and predominant cells are polymorphs.
  - It is less frequent with viral pneumonias. Here the effusion is small and predominant cells are lymphocytes.
- Parapneumonic effusions have three stages that represent a continuous spectrum. Most patients do not progress beyond the stage of simple parapneumonic effusion.
  1. Benign or sterile parapneumonic effusion, which arises due to increased permeability. It is exudative and is characterised by pH >7.20, glucose >60 mg/dL, negative Gram's stain and LDH less than three times the normal serum LDH.
  2. Complicated or infected parapneumonic effusion, characterised by pH <7.20. A complicated parapneumonic effusion with pH <7.20 and fluid glucose <60 mg/dL is usually purulent and Gram's stain positive. The causative organism can be grown in the culture. This grossly purulent effusion is then designated as "empyema".
  3. The third and final stage of pleural infection is the organising, fibrotic phase. During this fibrotic response pleural space may become focally or massively obliterated and is accompanied by the formation of dense fibrous adhesions. This process eventually results in a thick pleural peel that restricts chest mechanics and often necessitates a surgical decortication so as to address restrictive impairment.

Treatment

- Patients with benign parapneumonic effusion may be observed and a repeat tap is done if it persists or increases. If the free fluid separates the lung from the chest wall by >1 cm, a therapeutic thoracentesis should be performed.
- Treatment of underlying pneumonia should proceed on usual lines. Empirical anaerobic antibiotic cover is generally advised, as there may be an anaerobic co-infection. Choices in community-acquired empyema include amoxycillin with clavulanic acid or a combination of a second generation cephalosporin (e.g. cefuroxime) and metronidazole. Clindamycin monotherapy is an effective alternative for patients with a β-lactam allergy. Patients with nosocomial empyema need adequate Gram-negative cover. Possible choices include carbapenems, antipseudomonal penicillins (e.g. piperacillin/tazobactam), or third or fourth generation cephalosporins (e.g. ceftazidime and cefepime) with metronidazole. Vancomycin or linezolid may have to be added for suspected or proven methicillin-resistant *S. aureus* infections. Aminoglycosides demonstrate poor pleural penetration and reduced efficacy in acidic environments and should thus be avoided.
- Complicated parapneumonic effusion (empyema) should be treated by aspiration or thoracotomy tube drainage. If the fluid cannot be completely removed by thoracentesis, a thrombolytic agent (streptokinase—250,000 IU in 100 to 200 mL saline daily for up to 7 days; or urokinase—100,000 IU in 100 mL saline daily up to 3 days; or tissue plasminogen activator—10 to 25 mg twice a day for 3 days) may be instilled into the pleural cavity to break the fibrous septa. Decortication should be considered in patients with empyema who do not respond to conservative management.

Q. Write a brief note on chylous pleural effusion (chylothorax).

- Chylous pleural effusion results from leakage of chyle (thoracic duct lymph) into the pleural space. This is commonly associated with lymphomas, lung cancer with mediastinal spread, mediastinal fibrosis and following trauma.
- The pleural fluid appears milky and shows the characteristics of an exudate. Sudan III staining of the fluid shows fat globules. Total triglyceride level is more than 110 mg/dL. The cholesterol concentration is very low.
- Occasionally an empyema can be sufficiently turbid to be confused with chyle. They can be distinguished by centrifugation that leaves a clear supernatant in empyema while chylous effusion remains milky. However, in starved patients chyle may not appear milky.
- In the absence of trauma, a contrast-enhanced CT for mediastinal structures and a lymphangiogram are required.
- Treatment includes chest tube drainage and use of octreotide. Long-term tube drainage may produce malnutrition and immune deficiency. Therefore, if patient does not respond, a pleuroperitoneal shunt may be tried.

Q. Describe pseudochylous pleural effusion (pseudochylothorax).

- This is a rare condition where the pleural fluid appearance is similar to that of chylous effusion (milky).
- It is seen in long-standing benign pleural effusions—e.g. tuberculous effusion, rheumatoid effusion, etc.
- The pleural fluid appears milky. Cholesterol content of the fluid is very high (>200 mg/dL), which gives the fluid a milky appearance. Cholesterol crystals can be demonstrated in the fluid. Sudan III staining of the fluid does not show fat globules.

Q. Discuss eosinophilic pleural effusion.

- Pleural effusion with an eosinophil count of more than 10% of the total cells is known as eosinophilic pleural effusion. It is commonly seen in resolving infections (especially viral pneumonias and acute bacterial pneumonias), drug-induced effusion (e.g. nitrofurantoin, bromocriptine, amiodarone and phenytoin), hydropneumothorax, benign asbestos-related effusion, pancreatitis and trauma.
- Pleural fluid eosinophilia is uncommon in patients with cancer or tuberculosis unless the patient has undergone repeated thoracenteses.

Q. Discuss the aetiology, clinical features, investigations, complications and management of empyema thoracis.

Q. Discuss the management of non-tuberculous empyema.

Definition

- Empyema thoracis is in which pus and fluid from infection collects in the pleural cavity. It usually involves whole of the pleural space. If only a part of the pleural space is involved, it is called encysted or loculated empyema.

Aetiology

- Infection of pleural space from neighbouring structures—e.g. bacterial pneumonias, bronchiectasis, lung abscess, rupture of subphrenic abscess, oesophageal perforation and infection of haemothorax.
- Infection of pleural space from a distant source—e.g. bacteraemia.
- Infection of pleural space from external source—e.g. penetrating chest injury, chest tube placement and thoracic surgery.
- The common organisms involved are *Pneumococcus, Streptococcus, Staphylococcus, Pseudomonas, M. tuberculosis, H. influenzae* and anaerobes.

Clinical Features

- Patients with aerobic bacterial infection often present with acute onset of symptoms while immunocompromised or elderly patients or those with anaerobic infections present with chronic features.
- Systemic symptoms like high-grade, remittent fever with chills and rigors, malaise and weight loss.
- Respiratory symptoms like pleuritic chest pain, breathlessness and dry cough are present. Copious and purulent sputum indicates the presence of a bronchopleural fistula.
- Physical examination reveals digital clubbing, oedema of the chest wall, intercostal tenderness and signs of fluid in the pleural space.

Investigations

- Polymorphonuclear leucocytosis and raised ESR.
- Chest radiographic findings are similar to that of pleural effusion.
- Aspiration and examination of the pus.
  - The pus may vary from very thin to very thick in consistency.
  - The pus contains large numbers of polymorphonuclear leucocytes.
  - Gram staining may identify the organism.
  - The causative organism may be cultured from the pus.
  - Tubercle bacilli may be seen and culture for tubercle bacilli may be positive in tuberculous empyema.

Complications

- As a rule, complications occur in neglected cases where the pus is not fully removed from the pleural space at an early stage.
- The common complications of empyema are:
  - "Empyema necessitans"—the pus may track through and point on the chest wall.
  - Rupture through the chest wall forming a sinus.
  - Rupture into a bronchus may result in a bronchopleural fistula and pyopneumothorax.
  - Pleural fibrosis.
  - Metastatic brain abscess.
  - Amyloidosis.

Management of Empyema Thoracis

Non-Tuberculous Empyema

Acute

- Antibiotics should be administered based on the sensitivity of the organism. Empiric anaerobic coverage is often given.
- The pus in the pleural cavity should be drained in all cases. Daily aspiration of the fluid with a wide-bore needle can be attempted in an early and small empyema with thin fluid. Tube drainage is required in most cases. If this fails, limited thoracotomy or thoracoscopy is done. Thoracotomy involves resection of a small segment of the rib, clearing the empyema cavity and introducing a wide-bore tube for prolonged drainage.
- Intrapleural administration of fibrinolytic agents (e.g. streptokinase) is done in the case of presence of multiple septae.

Chronic

- Resection of an empyema sac in toto is the procedure of choice in a chronic empyema where no drainage procedure has been attempted before.
- Decortication is the procedure in a chronic empyema which has not responded to open drainage. The procedure involves stripping of whole of the grossly thickened visceral pleura. Thoracotomy allows the lung to re-expand and obliterate the pleural space.

Tuberculous Empyema

- Antituberculous chemotherapy.
- Repeated aspiration through a wide-bore needle or tubedrainage.
- Rarely, surgical treatment may be necessary.

Q. Discuss the aetiology, clinical features, types and management of pneumothorax.

Q. Describe tension pneumothorax.

Q. Write a short note on catamenial pneumothorax.

Q. What is clicking pneumothorax? Explain.

Definition

- Presence of air in the pleural cavity is known as pneumothorax.

Aetiology

- Primary (simple) spontaneous pneumothorax:
  - Commonly affects tall, slender males between the ages of 20 and 40 years who are smokers.
  - It is believed to be due to rupture of subpleural blebs at the lung apices.
  - The gradient of negative pleural pressure increases from the lung base to the apex so that alveoli at the lung apex in tall individuals are subject to significantly greater distending pressure than those at the base of the lung and this predisposes to development of apical subpleural blebs.
- Secondary spontaneous pneumothorax occurs in patients with known lung disease.
  - Rupture of emphysematous bullae.
  - Rupture of a subpleural tuberculous focus.
  - Rupture of a lung abscess, especially staphylococcal.
  - Bronchial carcinoma

- Pulmonary infarction
- Bronchial asthma
- ARDS
- Chest trauma
- Rare causes include sarcoidosis, *Pneumocystis jiroveci* pneumonia, lymphangioleiomyomatosis, Marfan's syndrome and cystic fibrosis.
- Catamenial pneumothorax (refer below).
- Traumatic pneumothorax:
  - Blunt and penetrating injuries to the chest wall, bronchi, lung or oesophagus
- Iatrogenic pneumothorax:
  - Following diagnostic or therapeutic interventions (e.g. secondary to transthoracic and transbronchial biopsy, central venous catheterisation, pleural biopsy and thoracentesis)

Clinical Features

- A small pneumothorax may be asymptomatic with no abnormal physical signs in the chest.
- Sudden onset chest pain and dyspnoea are the most common symptoms.
- Patients with secondary pneumothorax are more likely to be symptomatic because of the underlying lung disease.

Physical Signs

- General examination may reveal cyanosis, rapid thready pulse, pulsus paradoxus and signs of peripheral circulatory failure in severe cases.
- Inspection and palpation of respiratory system reveals tachypnea, shallow breathing, accessory muscles of respiration in action, shift of trachea and mediastinum (apex beat) to the opposite side, fullness of the chest on the affected side, diminished chest movements and markedly diminished vocal fremitus on the affected side. Measurements show a reduction in total chest expansion, increase in the size of the affected hemithorax, diminished expansion of the affected hemithorax and increased spinoscapular distance. Subcutaneous emphysema may be present.
- Percussion note is hyper-resonant over the affected hemithorax. In right-sided pneumothorax, liver dullness is obliterated and cardiac dullness is shifted to the opposite side.
- Auscultation reveals markedly diminished-to-absent breath sounds, absence of adventitious sounds and markedly diminished vocal resonance. In an open pneumothorax with a bronchopleural fistula, amphoric bronchial breathing may be heard. Coin test may be positive. Two coins when tapped on the affected side produce a tinkling resonant sound that is audible on auscultation.

Radiological Findings on Chest Radiograph

- Standard erect chest radiograph in inspiration is recommended for the initial diagnosis of pneumothorax rather than expiratory films.

- Mediastinal shift to the opposite side
- Sharply defined edge of the deflated lung
- Complete translucency and absence of bronchovascular markings in the area between the edge of the lung and chest wall
- Presence or absence of a complicating pleural effusion
- Presence or absence of underlying lung lesion

Ultrasonography

- It provides a rapid, sensitive and specific tool for the diagnosis of pneumothorax.

Types of Pneumothorax

- There are three types of spontaneous pneumothorax:
  1. Closed spontaneous pneumothorax
  2. Open spontaneous pneumothorax
  3. Tension (valvular) pneumothorax
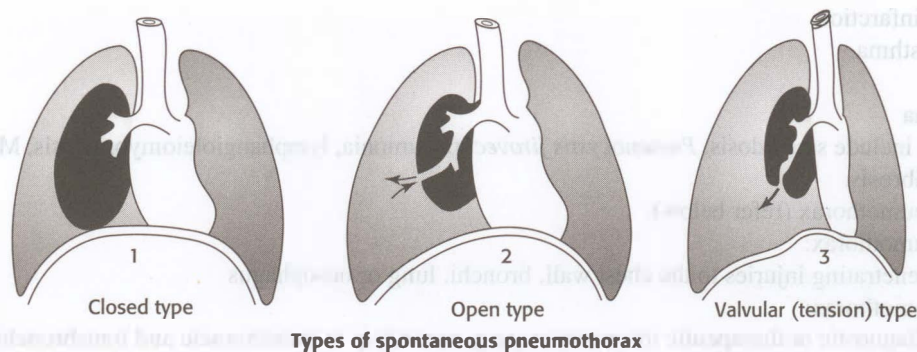
Types of spontaneous pneumothorax

Closed Spontaneous Pneumothorax

- The communication between pleura and lung seals off and does not reopen. Air can neither enter nor leave the pleural space. The trapped air is slowly re-absorbed and the lung reexpands completely in 2–4 weeks.
- Clinically, closed pneumothorax manifests as trivial breathlessness that gradually abates over a few days. Pleural space infection is uncommon.

Treatment

- Asymptomatic or slightly breathless patients with small pneumothorax (<2–3 cm from chest wall) need no treatment, but only serial radiographic monitoring is required till the lung re-expands. Spontaneous reabsorption of pneumothoraces has been estimated at 1.25% to 1.8% (about 50–70 mL) of the total volume of air in the pleural space per day. Administration of supplemental oxygen reduces the partial pressure of nitrogen in the pleural capillaries and increases air reabsorption from the pleural space.
- If the patient is breathless and the pneumothorax is large, it should be treated actively by one of the following methods:
  - Evacuation of the air using a syringe and needle, a three-way tap and an underwater seal system.
  - Inserting a chest tube into the pleural cavity and connecting it to a water seal drainage system or a non-return valve.

Open Spontaneous Pneumothorax

- The communication between bronchus and pleura does not seal off and remains patent, resulting in a "bronchopleural fistula". Since air can freely flow through the bronchopleural fistula, intrapleural pressure and atmospheric pressure remain the same throughout the respiratory cycle. This prevents the reexpansion of the collapsed lung. In addition, bronchopleural fistula facilitates spread of infection into the pleural space resulting in empyema.
- Open pneumothorax usually follows rupture of an emphysematous bulla, a small pleural bleb, a tuberculous cavity or a lung abscess into the pleural space.
- Clinically, the patient presents with breathlessness. If pleural space infection sets in, fever and systemic disturbances ensue. The physical signs are those of air and fluid in the pleural space (hydropneumothorax).

Treatment

- This form of pneumothorax usually requires surgical closure though a trial with chest tube insertion with low pressure suction may be tried. Various modalities of surgical closure are the following:
  - Cauterisation of the opening.
  - Video-assisted thoracoscopic surgery (VATS) may be used for cutting and release of adhesions that prevent the closure of the fistula.
  - Open thoracotomy and direct closure of the fistula.

Tension (Valvular) Pneumothorax

- The communication between pleura and lung persists. It acts as a one-way valve allowing air to enter the pleural space during inspiration, coughing, sneezing and straining, but not allowing it to escape. Large amounts of air gets "trapped" in the pleural space and the intrapleural pressure becomes much higher than the atmospheric pressure.
- The high intrapleural pressure results in compression of the underlying lung, as well as gross shift of the mediastinum to the opposite side with consequent compression of the opposite lung also. It also reduces venous return by compressing the vena cavae.

- Clinically, these patients present with rapidly progressive breathlessness, central cyanosis, rapid thready pulse and signs of peripheral circulatory failure. Frank signs of pneumothorax are present. Jugular venous distention is present. Death can occur within few minutes from asphyxia.
- Typical clinical situations where a tension pneumothorax may develop include the following:
  - Ventilated patients (invasive or non-invasive).
  - Traumatic chest injuries.
  - During cardiopulmonary resuscitation.
  - Lung disease, especially acute presentations of asthma and COPD.
  - Blocked, clamped or displaced chest drains.
  - Patients undergoing hyperbaric oxygen treatment.

Treatment

- Tension pneumothorax is an acute medical emergency.
- Emergency treatment is the introduction of a wide-bore plastic cannula in the second intercostal space, the other end of which is attached to a long rubber tubing, the end of which is placed underwater in a bottle.
- If patients is not haemodynamically compromised, alternative is the introduction of an intercostal catheter connected to a water seal drainage system.
- If nothing is available, simple stab on chest wall is sufficient to release pressure.

Recurrent Spontaneous Pneumothorax

- Recurrent episodes of pneumothorax are common in patients with emphysematous bullae. The episodes usually occur on the same side. It can also occur with LAM (lymphangioleiomyomatosis).
- The treatment includes obliteration of the pleural space by artificial pleurodesis. This can be accomplished by intra-pleural instillation of an irritant like tetracycline hydrochloride or talc powder. Alternatively, pleural abrasion or parietal pleurectomy may be attempted.

Catamenial Pneumothorax

- Most frequent symptom is thoracic endometriosis.
- A rare condition occurring in females over 25–30 years. Repeated attacks of spontaneous pneumothorax occur, usually on the right side, in association with menstruation. Attacks usually occur within 48 hours before or after the onset of menstruation. Haemoptysis may also occur.
- Various treatment modalities attempted include ovulation-suppressing drugs, surgical exploration and pleurodesis.

Clicking Pneumothorax

- A small left-sided pneumothorax may get localised in front of the pericardium. This may alter the heart sounds to make them sound loud and resonant ("clicking").

Q. What are the physical signs of hydropneumothorax?
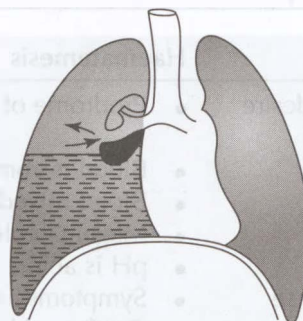
Hydropneumothorax with bronchopleural fistula

- Inspection and palpation:
  - Tracheal and mediastinal shift (apex beat) to the opposite side.
  - Fullness of chest on the affected side, with bulging of lower intercostal spaces.
  - Diminished chest movements and vocal fremitus on the affected side.
  - Affected hemithorax is usually bigger than the other.
  - Expansion of the affected hemithorax is reduced.
  - Spinoscapular distance is increased on the affected side.
- Percussion:
  - Percussion note is hyper-resonant over the upper air-containing part and stony dull over the lower fluid-containing part.
  - The upper border of the stony dullness is horizontal or straight. Shifting dullness can be elicited.
- Auscultation:
  - Breath sounds are absent over the entire hemithorax if there is no bronchopleural communication.
  - If a bronchopleural fistula is present, breath sounds are audible over the upper air-containing part. However, the intensity of breath sounds is diminished and it usually has an amphoric character.
  - Metallic crepitations may be heard over the upper air-containing part.
  - Vocal resonance is reduced over the entire affected hemithorax.
  - Coin test is positive over the upper air-containing part.
  - Succussion splash can be elicited on the affected side.

Q. How can you clinically differentiate pleural effusion from pneumothorax and hydropneumothorax?

Differentiating points	Pleural effusion	Pneumothorax	Hydropneumothorax
• Percussion note	Stony dull	Hyper-resonant	Hyper-resonant over upper part, stony dull over lower part
• Upper border of dullness	Highest laterally and lower anteriorly and posteriorly	—	Straight or horizontal
• Shifting dullness	Absent	—	Present
• Bronchial breathing	Tubular (above the level of effusion)	Amphoric (with BP fistula)	Amphoric (with BP fistula)
• Coin test	Negative	Positive	Positive
• Succussion splash	Absent	Absent	Present
• Aegophony and whispering pectoriloquy	Present above the level of effusion	Absent	Absent

Q. How will you differentiate haemoptysis from haematemesis?

Haemoptysis	Haematemesis
• Prodrome of tingling in the throat or a desire to cough	• Prodrome of nausea and abdominal discomfort
• Blood is coughed out	• Blood is vomited out
• Blood mixed with sputum	• Blood mixed with food particles
• Bright red and frothy blood	• Magenta coloured blood
• pH is normal as of blood	• pH is acidic
• Symptoms and signs of respiratory disease	• Symptoms and signs of gastrointestinal disease
• Confirmed by bronchoscopy	• Confirmed by upper GI scopy

Q. **Define haemoptysis. What are the common causes of haemoptysis?**

Q. **Outline the management of a case of haemoptysis.**

Q. **Discuss the management of massive (potentially lethal) haemoptysis.**

Definition

- Haemoptysis is defined as the expectoration of blood or bloody sputum.
- "Potentially lethal" or "massive" haemoptysis is defined as greater than 600–800 mL blood in 24 hours. A more clinical and practical definition of massive haemoptysis is any bleeding that results in a threat to life because of airway or haemodynamic compromise by bleeding.

Pathophysiology

- The lungs receive their blood supply via the pulmonary arterial circulation and the systemic bronchial arteries.
- More than 90% of cases of haemoptysis result from disruption of branches of bronchial arteries.
- Bronchial artery neovascularisation is the most common pathway for haemoptyisis and generally results from diseases that cause pulmonary arteriole occlusion from hypoxic vasoconstriction, thrombosis or vasculitis.
- In bronchitis or fungal infections, acute or chronic inflammation creates tortuous ectatic vessels through neovascularisation that are prone to rupture.
- Pulmonary parenchymal necrosis from necrotising pneumonia or infarction of lung from pulmonary embolism, inflammatory and immunologic vasculitides can also lead to haemorrhage by exposing the capillary bed.
- Haemoptyisis in tuberculosis has been discussed elsewhere.

Causes

Common causes	Uncommon causes
• Pulmonary tuberculosis	• Pulmonary thromboembolism
• Bronchial carcinoma	• Left ventricular failure
• Chronic bronchitis	• Mitral stenosis
• Bronchiectasis	• Bronchial adenoma
• Lung abscess	• Pulmonary arteriovenous malformations
• Pneumonia (particularly *Klebsiella*)	• Primary pulmonary hypertension
• Fungal infections (aspergilloma and invasive aspergillosis)	• Goodpasture's syndrome
	• Wegener's granulomatosis
• Pulmonary contusion/laceration (traumatic)	• Idiopathic pulmonary haemosiderosis
	• Haemorrhagic diathesis

- One recently identified cause of massive haemoptysis is the use of bevacizumab, a vascular endothelial growth factor angiogenesis inhibitor that when used in the treatment of central squamous carcinomas of the lung may result in massive haemoptysis.

Investigations

- In massive hameoptysis, initial diagnostic tests must begin in concert with efforts to stabilise the patient and control the bleeding.
- Blood should be examined for haemoglobin level, total and differential leucocyte counts, erythrocyte sedimentation rate (ESR) and blood group. In addition, clotting screen including platelet count should be done if a haemorrhagic diathesis is suspected.
- Urine should be examined by microscopy for red cells and red cell casts in suspected haemorrhagic diathesis and Goodpasture's syndrome.
- Sputum should be examined in all cases by microscopy and culture.
    - Ziehl–Neelsen staining may show acid-fast bacilli in pulmonary tuberculosis.
    - *Klebsiella pneumoniae* may be isolated from the sputum in Klebsiella pneumonia.

- Cytological examination for malignant cells in suspected bronchial carcinoma.
- Sputum studies may be helpful in identifying the pathogenic organism in acute exacerbations of chronic bronchitis, bronchiectasis and lung abscess.
- Chest radiographs, both posteroanterior and lateral views, can provide important diagnostic clues.
  - Presence of cystic lesions, ring shadows, tram tracks and grape clusters favour the diagnosis of bronchiectasis.
  - A distinct air-fluid level in a cavity is diagnostic of lung abscess.
  - Fibrotic bands, bronchiectatic changes, cavity formation or fluffy shadows in the upper lobes suggest pulmonary tuberculosis.
  - Rarely, an intracavitary aspergilloma is visible on chest radiograph as a cavity with a tumour-like opacity inside. A crescentic air shadow separates the fungal ball from the upper wall of cavity.
  - Upper lobe consolidation with bulging interlobar fissure is characteristic of Klebsiella pneumonia.
  - Bronchial carcinoma may manifest as central or peripheral pulmonary opacity, mediastinal widening, collapse of a lung or a lobe, or consolidation.
  - Chest radiographs can be useful at times in pulmonary thromboembolism, mitral stenosis, primary pulmonary hypertension, pulmonary haemosiderosis and bronchial adenoma.
- Computed tomography of the chest is useful in delineating lesions that are not seen on a plain radiograph. It also better defines the lesions seen on radiograph.
- Electrocardiogram may be useful in unsuspected mitral stenosis, pulmonary thromboembolism and pulmonary hypertension.
- Bronchoscopy is the most important diagnostic procedure. Rigid bronchoscopy permits visualisation of the more central airways, whereas fibreoptic bronchoscopy permits visualisation of the more peripheral airways. In addition to localising the site of bleeding, bronchoscopy provides definitive visual, biopsy or cytologic information.
- Isotope lung scans are useful if pulmonary embolism is suspected in a patient with a normal chest radiograph.

Treatment

Minor Haemoptysis

- Minor haemoptysis, which is scanty, will stop spontaneously without specific therapy. Treatment is aimed at the underlying cause.
- Substantial haemoptysis should be treated by keeping the patient calm, instituting complete bed rest and suppressing the cough. However, intubation and suction equipment should be ready at the bedside.

Potentially Lethal or Massive Haemoptysis

- Position the patient so that the side of the chest from which bleeding is arising is lowermost. This is to prevent asphyxiation due to aspiration of blood into the normal lung. If the location of bleeding is undetermined or the patient prefers, an upright position is also acceptable during this initial phase of management.
- Setup an intravenous infusion and collect blood for grouping and cross-matching. Maintain a chart of vital signs including blood pressure, pulse rate, respiratory rate and urine output.
- Administer oxygen.
- Blood transfusions are given according to the usual clinical guidelines of quantity of blood lost, haematocrit, blood pressure, pulse rate and urine output.
- Strong sedatives should be avoided, but mild sedatives may be given to relieve anxiety.
- Distressing cough may be suppressed with linctus codeine 15 mL thrice daily.
- Consider endotracheal intubation if the patient has poor gas exchange, has rapid ongoing haemoptysis, is haemodynamically unstable or has severe shortness of breath.
- An alternative strategy is to place an endotracheal tube into either the right or left mainstem bronchus. This is easier to achieve with bleeding from the left lung when selective intubation of the right mainstem bronchus is required.
- Double-lumen endotracheal tube allows the two lungs to be isolated and ventilated separately.
- Role of tranexamic acid, an antifibrinolytic agent, is controversial though most physicians would use it intravenously in massive haemoptysis.
- Consider emergency bronchoscopy if the bleeding is torrential.
  - The rigid bronchoscope is preferred as it enables blood to be aspirated more easily.
  - The fibreoptic bronchoscope may be used for cold saline lavage, which may sometimes arrest bleeding. The iced saline is instilled in 50- to 100-mL aliquots followed by suctioning and repeated until there is noticeable improvement. Other techniques used to control bleeding include:
    - Topical thrombin or fibrinogen.
    - Topical coagulation with laser photocoagulation (Nd:YAG).

- Argon plasma coagulator.
    - Endobronchial brachytherapy in high doses (10–12 Gy/hour for a total of 500–4000 Gy).
    - Endobronchial cryotherapy.
    - A balloon catheter passed through the bronchoscope can be inflated proximally in the bleeding bronchus. This will isolate the source of bleeding from the rest of the lung and the contralateral lung, preventing asphyxiation by blood flooding.
- Bronchial arterial catheterisation and embolisation can at least temporarily arrest bleeding. Embolisation is performed using absorbable gelatin sponge or polyvinyl alcohol particles between 325 and 500 μm. The most important complication is spinal cord ischaemia.
- Surgical intervention is indicated in selected cases. Emergency resection of the lobe or lung, which is bleeding, may be necessary.

Q. Discuss briefly the differential diagnosis of acute onset dyspnoea.

- Dyspnoea, defined as an uncomfortable awareness of breathing, is a subjective sensation for which there is no accurate objective measurement.
- Acute dyspnoea is defined as dyspnoea arising over the course of a few minutes to 24 to 48 hours.

Common Causes

- Cardiogenic pulmonary oedema
- Acute bronchial asthma
- Spontaneous pneumothorax
- Acute pulmonary embolism
- ARDS
- Laryngeal obstruction
- Hysterical hyperventilation syndrome

Differential Diagnosis

Cardiogenic Pulmonary Oedema

- History: A history of long-standing hypertension, ischaemic heart disease or valvular heart disease may be present. The characteristic symptoms of heart failure like exertional dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea and nocturia may precede the attack of acute breathlessness by days or weeks. Acute dyspnoea is usually associated with cough and pink frothy expectoration.
- Physical findings: Acute breathlessness is associated with profuse sweating, cyanosis, tachypnoea, tachycardia and pulsus alternans. There may be cardiomegaly with the apex beat shifted downwards and outwards, third heart sound (S_3) or a summation gallop. Examination of lungs reveals bilateral fine crepitations, predominantly basal. Other clinical evidences of long-standing hypertension (fundal changes and loud A_2 component of second heart sound), ischaemic heart disease (dyskinetic segment at or around cardiac apex, murmur of mitral regurgitation due to papillary muscle dysfunction and arrhythmias) or valvular heart disease (murmurs) may be present.
- The diagnosis can be confirmed by electrocardiogram, chest radiography, echocardiography and angiography.

Acute Bronchial Asthma

- History: Usually, previous history of similar attacks may be present. There may be family history of bronchial asthma, chronic eczema or allergic rhinitis in atopic individuals. A precipitating event like exposure to cold air or dust, respiratory infections, exercise, emotional stress, or intake of drugs like aspirin or propranolol may be identified.
- Physical findings: A severe attack is usually associated with cyanosis, tachycardia, tachypnoea and pulsus paradoxus.
- Examination of the respiratory system may reveal a hyper-resonant percussion note and extensive bilateral rhonchi. A very severe attack may be associated with a "silent chest".

Spontaneous Pneumothorax

- History: The usual history is sudden onset of chest pain and dyspnoea, usually following strenuous exertion or coughing. History related to a predisposing disease like emphysema, lung abscess, bronchial asthma, pulmonary tuberculosis or bronchial carcinoma may be present.
- Physical findings: The patient is usually severely dyspnoeic and tachypnoeic, with cyanosis, sweating, tachycardia, rapid thready pulse and signs of peripheral circulatory failure. Physical signs of pneumothorax include mediastinal shift

(apex beat and trachea) to opposite side, fullness of the affected hemithorax, diminished respiratory movements and diminished vocal fremitus and vocal resonance. The percussion note is hyper-resonant and cardiac dullness is shifted to the opposite side. Auscultation reveals markedly diminished to absent breath sounds. Physical signs related to the predisposing disease (refer history) may be evident.

- Diagnosis can be confirmed by chest radiography and ABG studies.

Acute Pulmonary Embolism

- History: A characteristic clinical setting such as prolonged immobilisation, recent surgery, congestive heart failure or recent trauma may be present. Oral contraceptives, sickle-cell anaemia and polycythaemia are associated with increased incidence of pulmonary embolism. The usual history is acute onset breathlessness and chest pain, occasionally associated with blood-tinged sputum.
- Physical findings: Respiratory findings include crepitations over the involved area, a pleural friction rub and evidence of pleural effusion. Cardiac findings include signs of right ventricular failure, including a right-sided third heart sound, early diastolic murmur of pulmonary regurgitation or increased intensity of the pulmonary component (P_2) of second heart sound.
- Diagnosis can be confirmed by electrocardiogram, chest radiography, echocardiography, lung scans and pulmonary arteriography.

Acute Respiratory Distress Syndrome (ARDS)

- History: Characteristic history is acute breathlessness in a patient with an underlying disease. The usual underlying causes are pneumonias, inhalation, and aspiration of toxic and irritant substances, septicaemia, eclampsia, DIC, lung embolism, trauma, certain drugs and acute pancreatitis.
- Physical findings: Dominant features are those of the underlying disease. There will be hypotension, hypoxaemia and bilateral crepitations, especially basal.
- Diagnosis can be confirmed by chest radiography and ABG studies.

Laryngeal Obstruction

- Acute laryngeal obstruction may follow anaphylactic reactions to drugs (penicillin, foreign proteins, etc.) and foreign body inhalation. Foreign bodies produce a picture of acute asphyxia characterised by cyanosis, stridor, violent but ineffective inspiratory efforts and indrawing of intercostal spaces. If untreated, the patient may progress to coma and death. Foreign body should be removed by direct laryngoscopy.

Hysterical Hyperventilation Syndrome

- History: This commonly occurs in young females, often associated with a recent emotional upset. In addition to acute dyspnoea, patients usually complain of tingling sensation around the mouth (circumoral paraesthesia), fingers and toes. Carpopedal spasms may occur.
- Physical findings: Physical examination reveals no evidence of cardiopulmonary disease. Tachypnoea and occasionally tachycardia may be present.

Q. What are the borders of Traube's space? How is it clinically significant?

- Traube's space is a semilunar area of tympanitic note, located at the left lower chest anteriorly. It is bounded by the normal lung resonance above, costal margin below, spleen on left side and left lobe of the liver on right side.
- Surface marking:
  - Draw two vertical lines one passing through the sixth rib in the midclavicular line and the next passing through the ninth rib in midaxillary lines.
  - Now draw a smooth curving line with convexity upwards from the sixth rib in midclavicular line to ninth rib in midaxillary line.
  - Draw another straight line passing through the costal margin from sixth rib to ninth rib.
- Traube's space is normally occupied by the fundus of stomach with air inside, which gives the tympanitic note on percussion (done from medial to lateral side).
- Traube's space is obliterated in pericardial effusion, pleural effusion, fundal tumours and enlargement of left lobe of liver or spleen. A left lung mass lesion/consolidation alone never produces impairment as lung is not extending to Traube's space.

Chapter 3

Immunological Factors in Disease

Q. What are the body's defence mechanisms?

- The first line of defence against pathogens is the epithelial barrier—skin and mucosa. Other first-line defences include commensal flora and acidic gastric contents.
- The second line of defence system is provided by the immune system. Cells of immune system originate from the stem cells in bone marrow. Immune system is divided into two functionally distinct systems:
  1. Innate or non-specific immune system
  2. Adaptive or specific immune system

Q. Discuss briefly about innate or non-specific immunity.

- It refers to inborn resistance to pathogens that does not require activation or adaptation upon exposure to a pathogen. The resistance is static, i.e. it does not improve with repeated exposure.
- Provides almost immediate protection against invading pathogens.
- Limited capacity to distinguish one microbe from another. Response is mostly focused on a limited set of microbial determinants shared by a large number of pathogens.
- Also plays a role in the induction of specific immune responses (e.g. release of cytokines and activation of complements that stimulate specific immunity).
- The innate immune system recognises molecular patterns common to many classes of pathogens; these elements have been termed as pathogen-associated molecular patterns (PAMP).
- The innate immune system recognises PAMP using a group of proteins termed as pathogen-recognition receptors (PRR).
- Toll-like receptors (TLR)
  - A particularly important group of PRR that are expressed on both innate immune cells and on cells in various tissues including endothelial cells, epithelial cells and fibroblasts.
  - TLRs expressed on cell surface recognise mostly bacterial products, while TLRs localised to intracellular compartments recognise mostly viral products and nucleic acids.
  - Binding of TLR to their microbial ligands leads to the activation of phagocytes and direct killing of pathogens, as well as to the release of pro-inflammatory cytokines and antimicrobial peptides.
  - In addition, these molecules activate dendritic cells and are therefore important in the initiation of adaptive immune responses.
- Other innate immune PRRs include retinoic acid-inducible gene-I-like receptors (RLRs) and nucleotide binding and oligomerization domain (NOD)-like receptors (NLRs).
- Due to limited diversity of PRRs, pathogens displaying a high mutation rate can easily escape recognition by the innate immune system. Moreover, ability of intracellular TLRs to kill several pathogens such as viruses is limited. Adaptive immunity is required for efficient immune response.

Components of Innate Immunity

Cells	Complement components
- Monocytes/macrophages - Dendritic/langerhans cells - Follicular dendritic cells - Large granular lymphocytes /natural killer cells (NK cells) - Neutrophils - Eosinophils - Mast cells - Basophils	**Cytokines** **Antimicrobial peptides** - Defensins - Cathelin

Cellular Components of Innate Immunity

Monocytes/Macrophages

- Monocytes arise from bone marrow and circulate in the blood.
- Macrophages arise from monocytes migrating to tissues.
- Their main functions are:
  - Binding to lipopolysaccharides released by bacteria.
  - Presentation of antigen to T lymphocytes.
  - Secretion of cytokines such as interleukin-1 (IL-1), tumour necrosis factor (TNF) and interleukin-6 (IL-6) that help in the activation of T and B cells.
  - Destruction of antibody-coated bacteria.

Dendritic/Langerhans Cells

- These are derived from bone marrow.
- These cells possess both class I and class II molecules on the surface (see HLA system) and are the most potent antigen-presenting cells (APCs) for T lymphocytes (both CD4 and CD8).

Follicular Dendritic Cells

- These are APCs for B lymphocytes.

Large Granular Lymphocytes (LGL)/Natural Killer Cells (NK Cells)

- LGLs mediate both antibody-dependent cellular toxicity and natural killer activity.
- Natural killer cells (NK cells) circulate in the blood but do not enter thymus to mature. NK cells do not have antigenic surface markers of T or B lymphocytes. They recognise and kill cells that become coated with antibodies such as tumour cells or cells infected with microbes. Their action does not require major histocompatibility complex (MHC) molecules and is therefore less specific than cytotoxic T cells. NK cells are part of both innate and adaptive immune systems.
- Upon stimulation, NK cells secrete large amounts of cytokines including interferon-γ (IFN-γ), tumour necrosis factor-α (TNF-α), granulocyte-macrophage colony-stimulating factor (GM-CSF) and several other chemokines.

Neutrophils, Eosinophils, Mast Cells and Basophils

- These cells produce inflammatory response to infection.
- They also phagocytose the microbial agents and cause their death. Efficient elimination of pathogens through phagocytosis requires rapid recruitment of effector cells to the infection site and this process is often referred to as the inflammatory response.

Complements

- These are a family of proteases produced by the liver and macrophages that circulate in inactive forms.
- These can be sequentially activated when it is bound to antigen–antibody complexes (classical pathway) or to the surface of a pathogen (alternative pathway).
- They damage cell membranes of pathogens and enhance recognition and killing by other immune system cells.

Cytokines

- These are soluble proteins secreted by a wide variety of cells. These are critical for both innate and acquired immune responses.
- Their functions include regulation of growth, development and activation of immune system cells and mediation of inflammatory responses.
- They may act in three manners: autocrine (action on the same cell that secretes them), paracrine (action on cells nearby to the cells producing them) and endocrine (action on distally located cells).
- Examples of cytokines in innate immunity are: interleukins (IL-1, IL-6, IL-12), interferons (INF-α, INF-β), tumour necrosis factor-α (TNF-α) and others.

Q. Describe the acquired immunity (specific or adaptive immunity). Antimicrobial peptides are not explained.

- Specific, acquired or adaptive immunity is characterised by antigen-specific responses to foreign antigens that take a few days to weeks to develop.

- It is mediated by T and B lymphocytes.
- Foreign substances that induce specific immune responses are called "antigens".
- Organs of immune system are lymphoid organs.
  - Lymphocytes are generated in primary lymphoid organs. These are bone marrow and thymus.
  - In secondary lymphoid organs, adaptive immune responses are initiated. These secondary lymphoid organs include lymph nodes, spleen and mucosa and gut-associated lymphoid tissues (MALT and GALT), i.e. tonsils, adenoids, appendix and Peyer's patches of small intestine.

Development of Lymphocytes

- All lymphocytes are derived from bone marrow stem cells.
- Lymphocytes enter the blood and are distributed either to thymus or to bone marrow. T lymphocytes are produced in the thymus while B lymphocytes (bursa-equivalent) are produced in the bone marrow.
- B lymphocytes differentiate into plasma cells when stimulated by antigen. Plasma cells produce immunoglobulins or antibodies that bind to the foreign antigen with high specificity.
- T lymphocytes recognise foreign antigens on the surface of host cells that include infected host cells and specialised host cells called APCs.

Antibody or Humoral Immune Response

- B lymphocytes mature in bursa of Fabricius in birds; hence named bursa-derived. In humans, they mature in bone marrow (bone marrow-derived).
- B lymphocytes are derived from stem cells in the bone marrow. The maturing pre-B cells remain in the marrow and express surface immunoglobulins (Ig).
- A process of selection then identifies the B cells with surface immunoglobulins that recognise self-antigens and these cells are disabled or eliminated. The surviving cells that will recognise foreign antigens enter the circulation and migrate to the lymphoid tissues.
- The B cells that are not exposed to a foreign antigen are naive cells. When these cells encounter an antigen, they are stimulated to undergo clonal expansion and become activated B cells. These cells release antibodies or immunoglobulins.
- B lymphocytes can bind foreign proteins, polysaccharides, lipids and other chemicals in extracellular or cell-associated forms.
- This first response to an antigen, the primary immune response is slow and not vigorous. During this response, IgM is secreted. Some cells from the activated clone become memory cells that circulate in the blood and remain dormant until they are re-activated by the same antigen. This second response is rapid and more vigorous and is known as secondary response. The immunoglobulin secreted is IgG, IgE or IgA.
- B cells also present antigenic peptides to T cells after processing the antigen.
- Although antibodies allow immune system to react with a large variety of antigens, these large molecules cannot cross the plasma membrane and are therefore unable to bind and destroy intracellular pathogens such as viruses.

Primary and Secondary Response

- When an individual is exposed to an antigen for the first time, there is a lag of several days before specific antibody becomes detectable. Initially, this antibody is of IgM class. After another few days, IgG antibody is formed.
- If at a later date the individual is exposed to the same antigen, there is a rapid appearance of much greater amount of IgG antibody. This is called secondary response. Thus, secondary response requires the phenomenon known as class switching of antibodies.

Primary response	Secondary response
• Slow in onset	• Rapid in onset
• Low in magnitude	• High in magnitude
• Short-lived	• Long-lived
• IgM antibody formed	• IgG (or IgA or IgE) antibody formed

Cell-Mediated Immune Response

- T lymphocytes develop from stem cells in the bone marrow but these cells migrate to thymus for maturation; hence are named T cells.
- In thymus, T cells proliferate and mature, acquiring a variety of cell-surface markers including T-cell receptor (TCR) and co-receptors (CD4, CD8 and others). In the thymus, T cells that recognise self-antigens are eliminated or disabled.
- Mature but naive T cells leave the thymus and migrate to secondary lymphoid follicles where they are exposed to antigens and become reactive T cells. T cells comprise 70–80% of circulating lymphocytes.
- T lymphocytes recognise only short peptide sequences in protein antigens that are present on the surfaces of other cells, bound to class I or II MHC proteins.
- TCR differ from B cell receptors. They are never secreted, existing instead on the cell surface as heterodimers of αβ or γδ subunits.
- These cells are classified into several subtypes based on their functions:
  - Cytotoxic T cells (T8 cytotoxic cells or CD8+ cells) comprise 25% of circulating T cells. They destroy host cells harbouring viruses and other foreign microbes.
  - Helper T cells (T4 helper cells or CD4+ cells) synthesise and secrete hormones called cytokines that activate the immune response in local populations of cytotoxic T cells, macrophages and B cells.
  - T-suppressor cells (generally CD4+) repress the immune response by inhibiting other T cells and B cells.
  - T-memory cells are clonal populations of T cells that have been exposed to antigen but do not become activated until subsequent exposure.
- T-helper cells have been further classified on the basis of cytokines they secrete:
  - Th1 cells respond to microbes and activate macrophages and natural killer cells and secrete IFN, IL-2 TNF and IL-10. These are efficient at activating macrophages and stimulating cytotoxic T cells, thereby inducing cell-mediated immunity. These cytokines may suppress Th2 response though INF-γ can stimulate Th2 response and antibody production.
  - Th2 cells respond to worms and allergens and secrete IL-3, IL-4, IL-5, IL-10 and IL-13. These cytokines activate B-cells producing humoral response.

Mechanism of Cell-Mediated Immune Response

- The first step is processing of antigens by APCs followed by presentation of processed antigens on the surface of these cells using the MHC on the cell surface.
- There are two distinct classes of MHC molecules:
  - Class I MHC molecules are expressed by most nucleated host cells. The class I proteins on the surface of infected host cells display foreign antigen (as peptide) and this is recognised by TCR of cytotoxic T cells that destroy the infected host cells. The TCR is very similar to immunoglobulin in structure, although it is encoded by a distinct set of genes. The diversity of TCRs is such that a given TCR is able to specifically react to a given peptide/MHC combination.
  - Class II MHC molecules are expressed by the APCs that include B cells and macrophages. These cells endocytose foreign proteins that are processed and then displayed on cell surface using the class II MHC. Helper T cells recognise the foreign antigens displayed by class II molecules and release cytokines that signal B cells to make antibodies against the foreign antigen and activate macrophages to destroy the ingested microbes.
- Other markers on the surface of T cells include co-receptors that increase the recognition of the MHC proteins. These include:
  - CD4 (CD–cluster of differentiation) is expressed on the surface of helper T cells and binds to class II MHC proteins on the APCs. It also functions as the receptor for human immunodeficiency virus.
  - CD8 is expressed on the surface of cytotoxic T cells and binds to class I MHC proteins on host cells. It is also expressed on T-suppressor cells.

Role of Other Cells and Proteins in Immune Response

- After lymphocytes are activated by antigens, several other cells and components, including those of innate immunity, get activated to enhance the immune response. These are:
  - Enhancing phagocytosis by macrophages and neutrophils.
  - Lysis and enhancing phagocytosis of microbes by complements.
  - Enhancing phagocytosis and stimulating further inflammatory responses by cytokines.

Cardinal Features of Immune Responses

- Specificity: Immune responses are specific for different antigens and in fact, for different structural components of a single protein, polysaccharide or other antigens. The portions of such antigens that are specifically recognised by individual lymphocytes are called determinants or epitomes. The total number of antigenic specificities of lymphocytes in an individual is called lymphocyte repertoire or repertoire of the immune system.
- Diversity: The lymphocyte repertoire is very large in an individual. It is due to an extreme variability in the structures of antigen-binding sites of lymphocytes. Therefore, body can respond to an extremely large number of antigens. This is known as diversity of immune system.
- Memory: As discussed above, secondary response occurs after re-exposure to the same antigen. This property of immune system is known as immunologic memory. Each exposure to an antigen expands the progeny of a particular antigen-responsive lymphocyte, i.e. it expands the clone of a lymphocyte specific for a particular antigen. These memory cells survive for long periods. The immune response of memory cells is rapid, larger and more efficient compared to the previous exposure.
- Self-tolerance: One of the important properties of immune system is its ability to respond only to foreign antigens (non-self) while not reacting to body's own antigens (self). This tolerance to self is discussed separately. A breakdown in this self-tolerance may lead to autoimmune diseases.

Q. Write a short note on the complement system.

- The complement system consists of a series of plasma proteins (β globulins). These are proteases in nature that play an important role in both inflammation and immunity.
- Complements are present as inactive forms in plasma (C1 to C9).
- It is a major constituent of the innate immune defence system that is also involved in the initiation of adaptive immunity.
- The major source of most circulating complement components is the liver. C1q production is mainly by bone marrow-derived cells like macrophages and dendritic cells.
- Three different pathways of complement activation:
  - Classical pathway
  - Alternative pathway
  - Lectin pathway
- These three pathways converge at the central component of the complement system, C3. The common pathway finally leads to the formation of a protein complex on a complement-activating surface named the membrane attack complex (MAC).

Classical Pathway

- Activated via binding of C1q to immunoglobulins (IgG and IgM), acute phase proteins, charged molecules, and apoptotic or necrotic cell debris.
- This results in activation of serine proteases C1r and C1s.
- C1s activates C4 and C2 leading to the formation of the C4b2a complex (C3 convertase) that leads to the activation of C3.

Alternative Pathway

- C3 produced in the liver is cleaved into C3a and C3b by enzymes in the blood.
- If there is no pathogen in the blood, C3a and C3b protein fragments will be deactivated.
- If there is a nearby pathogen some of the C3b is bound to plasma membrane of the pathogen and will then bind to factor B.
- This complex is then cleaved by factor D into C3bBb, which is the alternative pathway C3 convertase.
- This convertase is stabilised by properdin and can subsequently activate C3.
- Activated C3 can bind with factor B and the subsequent activation of factor B leads to the formation of a more active C3 convertase, C3bBb.

Lectin Pathway

- Activation occurs in response to the recognition of mannose-binding lectin (MBL) and ficolins (L-ficolin and H-ficolin) of various carbohydrate ligands instead of C1q as in classical pathway.
- This pathway is activated by binding of MBL to mannose residues on the pathogen surface, which activates the MBL-associated serine proteases (MASP), MASP-1 and MASP-2. These then split C4 into C4a and C4b and C2 into C2a and C2b. C4b and C2a then bind together to form C3 convertase.

Terminal Pathway

- Incorporation of C3b molecule in the C3 convertases leads to the formation of C5 convertase.
- C5 is activated and subsequent binding of C6, C7, C8 and C9 results in the formation of the MAC C5b-C9.
- During complement activation, cleavage fragments of complement components are generated that include anaphylotoxins C3a, C4a and C5a. These low molecular weight peptides have the ability to bind to mast cells and basophils and release histamine and other highly active peptides. These peptides increase permeability of the vascular walls allowing neutrophils to migrate into the area.
- C5a is a potent chemotactic (attractant) factor.
- C4b and C3b can opsonise particles by binding to the surface leading to the recognition of these particles by phagocytes.

```
        Alternative            Lectin              Classical
        Pathogen          Serum lectins bind    Antigen–antibody
         surface          mannan on pathogen         complex

           C3              MBP:MASP1,2              C1 (q,r,s)
           B                   C4                       C4
           D                   C2                       C2

                    C3 Convertase (C4b2a, C3bBb)

                               C3

        C4a              C3b ───────────► C5b
        C3a           Opsonisation         C6
        C5a                                C7
                                           C8
                                           C9
   Mediators of inflammation,
    phagocyte recruitment        Membrane attack complex, lysis of cells
```

Three different pathways of complement activation
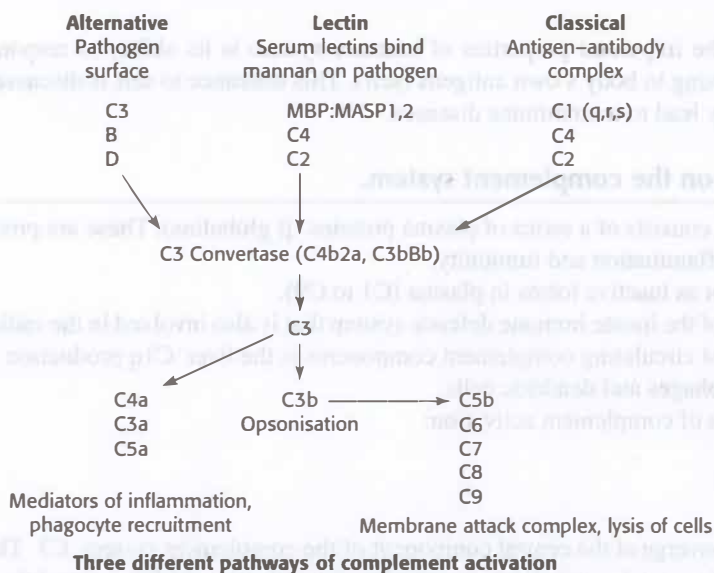
Complement System in Diseases

- Complement system might play a role in many diseases with an immune component, such as asthma, lupus erythematosus, membranoproliferative glomerulonephritis, multiple sclerosis and inflammatory bowel disease.
- Deficiencies of the terminal pathway predispose to both autoimmune diseases and infections (particularly *Neisseria meningitidis*). C3 (C1, C2 and C4) deficiency predisposes to life-threatening pyogenic infections and early death.

Q. Briefly discuss immunoglobulins.

- Immunoglobulins are end products of plasma cells that develop on the stimulation of B lymphocytes by an antigen. They are humoral mediators of immunity.
- Antibodies or immunoglobulins bind to a specific portion of antigen called epitome. Thus, an antibody recognises one epitome rather than whole antigen.
- Various immunoglobulin classes are IgG, IgA, IgM, IgD and IgE.
- There are four subtypes of IgG: IgG1, IgG2, IgG3 and IgG4.
- Immunoglobulin molecule has two subunits—two light chains and two heavy chains that are linked by disulphide bonds (S–S).
- Light chains exist in two classes, lambda (λ) and kappa (κ). Each antibody molecule has either λ or κ chains, not both.
- There are five different heavy chains (α, γ, δ, ϵ and μ) . The type of heavy chain determines the class or isotype of the antibody molecule, i.e. IgA, IgG, IgD, IgE and IgM antibodies.
- IgA exists in monomeric and dimeric forms, whereas IgM exists in pentameric form. Additionally, IgA molecules receive a secretory component from the epithelial cells into which they pass.

- The enzyme papain cleaves the Y-shaped immunoglobulin molecule at the hinge region into two parts:
  - Fab region—antigen binding site.
  - Fc region—binds to surface Fc receptors of macrophages, neutrophils and eosinophils.
- The heavy and light chains are each made up of variable (V) and constant (C) regions (e.g. VH, CH—variable and constant regions of heavy chain. VL, CL—variable and constant regions of light chain).

Structure of immunoglobulin molecule
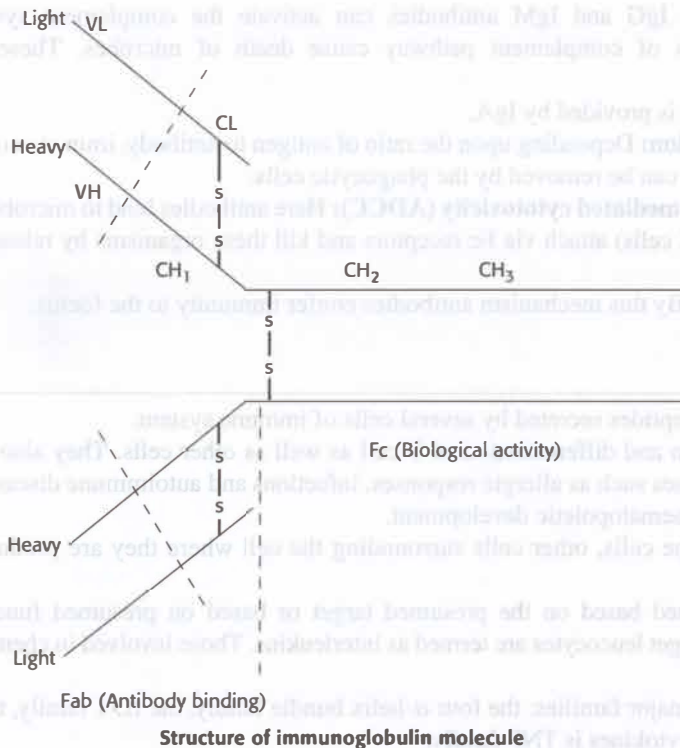
Chart for Immunoglobulins

• **IgG – 70%**	Found in serum and ECF; opsonisation of antigens for phagocytosis, complement fixation by activating classical pathway, antibody-dependent cell killing by NK cells and macrophages and blocks viral entry into cells; directed against proteins; transplacental transfer
• **IgA – 20%**	Secretory type involved in mucosal and epithelial defence
• **IgM – 10%**	Macromolecular, having complement fixing activity; binds foreign antigens to initiate antibody production; produced in response to polysaccharide antigens; secreted during primary response
• **IgD – <0.5%**	Lowest level in serum; exact function not known
• **IgE – <0.5%**	Considerable affinity to mast cells and basophils; involved in immediate (anaphylactic) hypersensitivity

Q. Describe the functions of immunoglobulins.

- **Processing antigen:** Antibodies present on B cells help in interiorisation of antigen and further processing it for presentation to other cells.
- **Agglutination:** Antibodies help in agglutination of particulate matter including bacteria and viruses. IgM is particularly suitable for this function.

- **Opsonisation:** It implies coating of bacterial surface for which the Fab region of antibody has specificity. This facilitates subsequent phagocytosis by cells possessing Fc receptor (e.g. neutrophils).
- **Neutralisation:** Some antibodies neutralise the toxins released by bacteria. Some antibodies can hinder the ability of viruses to attach to receptors on host cells.
- **Immobilisation:** Antibodies against bacterial cilia or flagellae hinder their movement and ability to escape the phagocytic cells.
- **Complement activation:** IgG and IgM antibodies can activate the complement system by classical pathway. The terminal components of complement pathway cause death of microbes. These components also help in phagocytosis.
- **Mucosal protection:** This is provided by IgA.
- **Immune complex formation:** Depending upon the ratio of antigen to antibody, immune complexes of varying sizes are formed. Larger complexes can be removed by the phagocytic cells.
- **Antibody-dependent cell-mediated cytotoxicity (ADCC):** Here antibodies bind to microbes via their Fab region. Large granular lymphocytes (NK cells) attach via Fc receptors and kill these organisms by release of toxic substances called perforins.
- **Transplacental passage:** By this mechanism antibodies confer immunity to the foetus.

Q. What are cytokines?

- Cytokines are small polypeptides secreted by several cells of immune system.
- They promote proliferation and differentiation of T cell as well as other cells. They also play a critical role in many pathophysiological processes such as allergic responses, infectious and autoimmune diseases, angiogenesis, inflammation, tumour growth and haematopoietic development.
- These may act on the same cells, other cells surrounding the cell where they are produced or on cells present at a distant site.
- Cytokines have been named based on the presumed target or based on presumed functions. Those cytokines that are thought to primarily target leucocytes are termed as interleukins. Those involved in chemotaxis of inflammatory cells are termed chemokines.
- Cytokines belong to four major families: the four α-helix bundle family, the IL-1 family, the IL-17 family and chemokines. Another important cytokines is TNF family.
- The four α-helix bundle family has three subfamilies each with several cytokines:
  - IL-2 subfamily: IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-11, IL-12, IL-13, IL-15, IL-21, IL-23, granulocyte-macrophage colony-stimulating factor, erythropoietin, etc.
  - Interferon subfamily: IFN-β and IFN-α.
  - IL-10 subfamily: IL-10, IL-19, IL-20, IL-22, IL-24 and IL-26.
- All chemokines signal through seven transmembrane domain and G-protein coupled receptors. To date, more than 40 distinct chemokines have been well characterised. Important chemokines include granulocyte chemotactic protein 2 (GCP-2), stromal cell-derived factor 1 (SDF-1), neutrophil activating peptide 2 (NAP-2), macrophage inflammatory protein 1 (MIP-1), monocyte chemoattractant protein (MCP-1, MCP-2, MCP-3, MCP-4), macrophage inflammatory protein (MIP) and RANTES (regulated on expression, normal T cell expressed and secreted).
- Interleukin-1 (IL-1), interleukin-2 (IL-2), interferons (IFNs) and TNF are the key groups of cytokines that carry out the most important functions.

Interleukins

- IL-1 is produced by macrophages. Its main effects are fever, bone marrow release of neutrophils, T cell and neutrophils chemotaxis, B cell proliferation and antibody production and production of IL-2 by T cells.
- Interleukin-2 (IL-2) stimulates the proliferation of activated B cells, T cells and NK cells.

Tumour Necrosis Factor-α

- TNF-α is produced by macrophages in response to infection by bacteria and other microbes. Its functions are:
  - It promotes the production of more cytokines including IL-1.
  - It enhances the stimulation of T and B cells and other immune system cells to make a response to antigenic challenge more potent.
  - It also increases the expression of MHC class I and class II molecules and so improves antigen presentation.
  - It is an antiviral cytokine.

- It has antitumour properties.
- It can adversely affect endothelial cells that can produce ARDS, disseminated intravascular coagulation (DIC) and acute renal failure.

Interferons

- Interferons include interferon-alpha (IFN-α), interferon-beta (IFN-β) and interferon-gamma (IFN-γ).
- IFNs are produced by a wide range of cells when under attack from viruses and other non-self pathogenic antigens.
- IFN-γ is mostly released by activated T-cells.
- All IFNs act largely in synergy with IL-1 and TNF to promote resistance to pathogenic attack.
- IFNs promote expression of MHC class I and class II molecules improving antigenic presentation.

Q. Give a brief account of inflammatory response.

Q. Describe acute phase reactants.

Q. Explain erythrocyte sedimentation rate.

- Inflammatory response is a protective response of tissues to injury, irritant or infection and is required to remove the injurious stimuli as well as initiate the healing process.
- Tightly regulated to prevent continuous response.
- Classified as either acute or chronic.
- Acute inflammation.
    - Initial response of the body to harmful stimuli.
    - Involves local vascular system, immune system and various cells within the injured tissue that results in infiltration of phagocytic cells and increase in enzymes (e.g. cyclo-oxygenase, inducible nitric oxide) within the tissues. These result in release of leucotrienes, prostaglandins, histamine, kinins and nitric oxide, producing vasodilatation and increased local vascular permeability. In addition, cytokines like IL-1, IL-6 and TNF-α produced at the site of inflammation have systemic effects including the production of acute phase reactants.
    - Acute inflammation is characterised by classic local signs of inflammation—swelling, redness, pain, heat and loss of function.
    - Systemic features occur due to release of cytokines and are shown below:

CNS	Respiratory
• Fever, sweating (due to change in hypothalamic set point)	• Tachypnoea
• Headache	**Endocrine**
• Confusion	• Increased secretion of catecholamines
• Anorexia	• Increased secretion of glucocorticoids
Liver	• Increased secretion of insulin
• Increased synthesis of acute phase reactants	**Others**
Cardiovascular	• Increased production of neutrophils
• Tachycardia	• Flushing
• Hypotension	• Enlarged draining lymph nodes

- Outcomes of acute inflammation:
    - Complete resolution.
    - Fibrosis.
    - Abscess formation.
    - Chronic inflammation.
- Chronic inflammation:
    - Progressive shift in the type of cells that are present at the site of inflammation.
    - Characterised by simultaneous destruction and healing of the tissue.
    - Inflammatory cells include lymphocytes, macrophages and plasma cells.

- Exudation of fluid is not significant.
- Continued tissue necrosis may occur.
- Granulomatous inflammation occurs in context of foreign materials and infectious agents resistant to phagocytosis.
- Typically seen in tuberculosis and leprosy.

Investigations

- Leucocytosis, increased platelet counts.
- Elevated erythrocyte sedimentation rate (ESR).
- Elevated acute phase reactants or proteins.
- Normocytic and normochromic anaemia in chronic inflammation.

Erythrocyte Sedimentation Rate

- Measures the rate of fall of red blood cells through plasma.
- Normally, red cells do not aggregate because of their repellant negative charge. Plasma proteins that are positively charged neutralise the surface charge of red cells. Elevation in plasma proteins, particularly fibrinogen, causes aggregation of red cells forming rouleaux. Rouleaux have a higher mass/surface area ratio than single erythrocyte and thus fall faster, leading to elevated ESR.
- ESR is elevated in acute inflammation where levels of acute phase reactants are increased. Due to increased levels of fibrinogen, ESR is elevated in pregnancy, old age and chronic renal failure. Also elevated in many other conditions where there is no alteration in acute phase reactants. For example, ESR is increased in conditions associated with monoclonal (multiple myeloma) or polyclonal (chronic infections) increase in immunoglobulins. In systemic lupus erythematosus (SLE), ESR is elevated while CRP may be normal.
- ESR may be low if plasma proteins are low or red cell morphology is abnormal, thereby making rouleaux formation impossible. Examples include hereditary spherocytosis, sickle cell anaemia and microcytic anaemia.

Acute Phase Reactants

- These are proteins produced by liver in response to inflammatory stimuli and play an important role in host defence and stimulate repair and regeneration.
- Include C-reactive protein, fibrinogen, α-1 antitrypsin, haptoglobin, manganese superoxide dismutase, iron-binding proteins (ferritin, transferrin, lactoferrin), serum amyloid A and serum amyloid P.
- In chronic inflammation, these proteins may contribute to the development of amyloidosis.

C-Reactive Protein (CRP)

- Levels increase within 6 hours of acute inflammation and fall within a few days after inflammation subsides.
- Therefore, sequential measurement is useful in monitoring the disease activity.
- Some inflammatory diseases are associated with normal or slightly elevated levels of CRP. These include SLE, scleroderma and ulcerative colitis. However, concurrent infection in these conditions produces significant elevation of CRP levels.

Q. What is tolerance? Explain briefly.

- It is an active physiological process producing immunological unresponsiveness to an otherwise immunogenic substance. It involves both humoral- and cell-mediated immunity.
- Possible mechanisms are:
  - Elimination of self-reacting T and B cells.
  - Disabling self-reacting T and B cells.
  - Presence of T-suppressor cells that are antigen specific.
  - Presence of antibodies that alter self-antigen such that they are no longer susceptible to an immune response.
  - Sequestration of antigens.

Q. Describe autoimmunity.

- It indicates development of immune reaction against self-antigens.
- Postulated mechanisms of autoimmunity are:
  - Failure of suppression of self-reacting T and B cells.
  - Tissue damage resulting in the release of sequestered antigens.

- Tissue damage altering the antigenic structure.
- Shared immunologic epitope with a microbe and the host (molecular mimicry).
- Infection altering cell-surface markers in a genetically susceptible individual.
- Persistent viral infections leading to immune-mediated injury due to constant presence of viral antigen driving the immune response.
- Decline in T-suppressor cells.

Q. What are the different types of immune reactions?

- Immunologically mediated reactions are of five types that may result in tissue damage. They can be summarised as follows:

Type	Prototype disorder	Immune mechanism
I Anaphylactic type or immediate hypersensitivity type	Anaphylaxis, urticaria, angio-oedema, bronchial asthma, allergic rhinitis	• Formation of IgE antibody leading to release of vasoactive amines and other mediators from basophils and mast cells; not all type I reactions are anaphylactic • Very small amounts of an allergen seem to be sufficient to allow interaction and cross-linking of receptor-bound IgE molecules
II Cytotoxic type	Autoimmune haemolytic anaemia, Goodpasture's syndrome	• Formation of IgG (occasionally IgM) antibodies that bind to antigen on target cell surface (red cells, leucocytes, platelets, etc.) and activate complement system via classical pathway, leading to phagocytosis or lysis of target cell. This reaction is also known as antibody dependent cellular cytotoxicity (ADCC)
III Immune complex type	Serum sickness, Arthus reaction, SLE, Henoch-Schonlein purpura, immune-complex type of glomerulonephritis, transfusion reactions	• Antigen–antibody complex (immune complex) deposition in microcirculation → complement activation → neutrophil chemotaxis → release of lysosomal enzymes and other toxic moieties → tissue destruction
IV Cell-mediated (delayed) type	Tuberculosis, transplant rejection	• Sensitised T lymphocytes → release of cytokines, T cell-mediated cytotoxicity; independent of antibody production; reaction appears in 18–24 hours with maximal response at 48–72 hours
V Stimulatory antibody mediated	Graves' disease	• Long-acting thyroid stimulator (LATS)

Q. Define allergy.

- Allergy is a state of hypersensitivity induced by exposure to a particular antigen, generally environmental. This antigenic substance capable of producing a type I, IgE-mediated immune response is called an allergen. The first dose of allergenic exposure—priming dose—sensitises the immunologic system (B lymphocyte). Subsequent exposures—shocking dose—result in a harmful immunologic activation and the ultimate expression of an "allergic reaction".
- Common reactions include asthma, rhinitis, urticaria, angio-oedema, eczema, food hypersensitivity and anaphylaxis.

Q. Explain urticaria or hives.

- Formation of "wheal-and-flare" cutaneous lesions involving only the superficial portions of the dermis. This results in circumscribed wheals with erythematous, raised and serpiginous borders with blanched centres.
- The lesions vary in size from one millimetre to several centimetres.
- Almost always pruritic and usually last for a few to 24 hours. When individual lesions last more than 36 to 48 hours and leave post-inflammatory hyperpigmentation or palpable purpura, diagnosis of urticarial vasculitis is more likely. Some

lesions may last for several weeks. Those lasting up to 6 weeks are classified as acute urticaria while those persisting beyond 6 weeks are classified as chronic urticaria.
- Fresh lesions may appear as the older ones fade.
- May be associated with headache, dizziness, nausea, vomiting, abdominal pain, diarrhoea and arthralgias. In most severe form, it may be associated with anaphylaxis.
- Pathogenesis involves degranulation of mast cells, which may be induced by immunologic or non-immunologic mechanisms, and subsequent release of histamine and various cytokines leading to oedema. Non-immunological mast cell activation may occur via substances such as neuropeptides (e.g. substance P), drugs (e.g. morphine, codeine, vancomycin), foods (e.g. strawberries) and radiocontrast media.
- Types of urticaria (based on aetiopathogenesis):

Immunologic	Physical
• IgE dependent	• Dermatographism
• Autoimmune	• Delayed pressure
• Immune complex mediated	• Cold
• Contact	• Localised heat
• Complement dependent	• Cholinergic
Non-immunologic	**Idiopathic**
• Direct mast cell-releasing agents	
• NSAIDs, ACE inhibitors	

Q. Discuss the clinical features and treatment of angio-oedema.

- An IgE-mediated reaction to a variety of allergens presents as well-demarcated oedema involving the deeper layers of skin as well as subcutaneous and submucosal tissues.
- May occur at any age but most commonly affects young adults.
- Acute angio-oedema lasts for up to 6 weeks; chronic angio-oedema beyond 6 weeks.
- Most cases are idiopathic. May occur due to insect sting, drug reaction, food allergy and exposure to other biological products. It can also occur due to direct release of histamine from the mast cells. Rarely, angiotensin-converting enzyme (ACE) inhibitors can cause angio-oedema.
- Hereditary angio-oedema, an autosomal dominant disorder, is due to the deficiency of production of C1-esterase inhibitor, a complement protein that inhibits spontaneous activation of classical complement pathway. Angio-oedema occurs either spontaneously or following infection or injury particularly dental injury. Onset is usually in early childhood but it can begin during adulthood also. The attacks become worse at puberty and usually decrease in frequency and severity after the age of 50 and may even disappear totally. Diagnosis confirmed by low levels of C1-esterase inhibitor (in 85% cases) or dysfunctional C1-esterase inhibitor (in 15% cases). C4 levels are also low while C1q levels are normal.
- Acquired C1-esterase inhibitor deficiency can present very similarly to the hereditary angio-oedema, but the onset occurs in the fifth and sixth decades of life. Both C1-esterase inhibitor and C1q levels are low. May occur with B-cell lymphoma, multiple myeloma, Waldenstrom's macroglobulinaemia and chronic lymphocytic leukaemia.
- ACE inhibitors usually produce angio-oedema due to increased bradykinin levels. Most cases occur within 3 weeks of starting treatment, but can occur at any time during treatment. It usually affects the face and oral mucosa and can cause serious breathing difficulty.

Clinical Features
- Presents with well defined, non-pitting swelling, usually nonpruritic.
- In a large proportion of patients, it is associated with urticarial lesions.
- May involve any area of the body and may occur as single or multiple lesions. Characteristically, the peri-orbital, peri-labial and genital areas are involved.
- Involvement of tongue and pharynx may produce dysphagia.
- Stridor, hoarseness, dysphagia and drooling indicate impending airway compromise.
- Angio-oedema of intestines may produce severe abdominal pain.

Treatment

- Remove the offending agent if possible.
- Control an acute attack with epinephrine.
- Administer high doses of antihistamines to control the lesions, e.g. diphenhydramine in a dose of 50 mg four times a day.
- Observe the patient for any evidence of airway obstruction. Manage patients with features of airway obstruction in a fashion similar to those with anaphylaxis.
- In patients with chronic angio-oedema not responding to antihistamines used in maximal dosages, glucocorticosteroids and other immunomodulating agents (e.g. methotrexate, cyclosporine and intravenous immunoglobulins) may be considered.
- During severe attacks of hereditary angio-oedema, fresh frozen plasma (or plasma-derived Cl-esterase inhibitor concentrate) is life saving as it provides Cl-esterase inhibitor. Recombinant Cl-esterase inhibitor is available in some countries, and is used for both treatment and prophylaxis. Ecallantide, a kallikrein inhibitor and icatibant, a bradykinin-receptor antagonist are also approved for treatment of acute attack. Antihistamines and steroids are not effective. Danazol is useful to prevent episodes of hereditary angio-oedema.

Q. What are anaphylactic reactions?

Q. Discuss briefly anaphylactoid reaction.

- Anaphylactic reaction is a prototype example of a type I hypersensitivity immunologic reaction that is IgE mediated.
- Prior sensitisation to inciting antigen, either alone or in combination with a hapten, is required. This initial event results in the synthesis of specific IgE, which attaches to mast cells and basophils. Subsequent exposure to the antigen produces IgE-induced degranulation of mast cells and basophils resulting in the liberation of a number of active substances. These include:
  - Histamine
  - Leucotrienes (LTC_4, LTD_4, LTE_4)
  - Prostaglandins
  - ECF-A (eosinophil chemotactic factor of anaphylaxis)
  - Kinins
  - NCF (neutrophil chemotactic factor)
  - Platelet-activating factor
  - Heparin.
- The release of these mediators of inflammation is responsible for the pathogenesis of an anaphylactic reaction.
- Common allergens that can produce anaphylaxis (or angio-oedema) are given below:

Drugs
- Antibiotics (penicillins, cephalosporins, tetracyclines, trimethoprim-sulphamethoxazole, vancomycin, nitrofurantoin)
- Chemotherapeutic agents
- Insulins
- Vitamin B1 and folic acid
- Diuretics and β-blockers
- Intravenous anaesthetic agents (suxamethonium, propofol)

Biological agents
- Blood and its components
- Tetanus, rabies and diphtheria antitoxins
- Antithymocyte globulin
- Vaccines

Proteins
- Foods (peanuts, fish, egg, milk, soy products)
- Preservatives like sulphites
- Food additives (aspartame, monosodium glutamate)

Insect bites and stings
- Honey bee
- Wasps

- Anaphylactic reactions have 3 basic patterns: uniphasic, biphasic and protracted reactions.
  - A uniphasic reaction occurs as an isolated reaction producing signs and symptoms typically within 30 minutes of exposure to an offending allergen and resolving usually within 1-2 hours.
  - In biphasic reaction, initial reaction is followed by occurrence of second wave of symptoms after resolution (spontaneously or with treatment) of the first phase. Most biphasic reactions occur within 8 hours of the first symptoms.
  - A protracted reaction may last for a prolonged period of time.
- Anaphylactoid reactions (pseudo-allergic reactions) are indistinguishable from anaphylactic reactions. However, these reactions involve IgG and IgM antibodies and not IgE antibodies. These antibodies activate the complement system through classical pathway that results in the formation of activated complements. Further, there may be direct release of preformed mediators from mast cells and basophils. Reaction may occur on first exposure to an agent. The radiographic contrast reactions are typically anaphylactoid reactions. Other causes of anaphylactoid reaction include use of opiates, aspirin, vancomycin, plasma expanders and quinolones, exposure to cold and exercise.
- Within minutes to hours of antigenic exposure, the following clinical symptoms may occur due to anaphylaxis.

Mucocutaneous	Gastrointestinal
- Pruritus	- Nausea, vomiting
- Flushing	- Abdominal cramps
- Urticaria	- Diarrhoea
- Angioedema	**Cardiovascular**
- Conjunctival injection	- Tachycardia
Respiratory	- Hypotension
- Bronchospasm resulting in chest tightness, dyspnoea and wheeze	- Arrhythmias
- Laryngeal oedema resulting in stridor	- Shock and collapse
- Pulmonary oedema	

- Insect stings:
  - Yellow wasps do not lose their stinger and the sting site frequently becomes infected. On the other hand, honeybees lose their stinger that may be implanted at the site of a sting.
  - Clinical features of anaphylaxis induced by insect sting are similar to the ones produced by other causes.
  - The most common reaction to insect stings is local reaction (erythema, itching, pain and swelling). Multiple stings (50–100 simultaneously) may produce toxic reaction in the form of nausea, vomiting, diarrhoea, light-headedness and syncope but without urticaria, bronchospasm and angio-oedema.
  - Occasionally, haematological, renal and neurological features are also seen after the insect sting but these are not related to IgE-mediated reactions.
  - Delayed reaction can occur in three forms: early delayed reaction (urticaria, arthritis and pedal oedema) within 6–24 hours, reaction within 24–72 hours (skin rash and urticaria) and serum sickness after 10–14 days.

Diagnosis

- With unknown allergen or an acute onset of illness with:
  - Development of mucocutaneous features with one of the following:
    - Respiratory compromise
    - Reduced blood pressure or end-organ dysfunction (e.g. collapse, syncope, incontinence)
- After exposure to likely allergen, rapid occurence of ≥2 of:
  - Development of mucocutaneous features
  - Respiratory compromise
  - Reduced blood pressure or end-organ dysfunction (e.g. collapse, syncope, incontinence)
  - Persistent gastrointestinal features
- After exposure to known allergen:
  - Rapid fall in blood pressure

Treatment

- Epinephrine is the first treatment to be given to patients with anaphylaxis. 0.2–0.5 mL of a 1:1000 solution epinephrine is given intramuscularly (lateral aspect of thigh) and repeated at 5–10 minutes intervals if response is inadequate. In severe cases, 1 mL of 1:100,000 of solution is given intravenously over 2–10 minutes.
- IV line.
- Oxygen 4–6 L/minute.
- Endotracheal intubation or tracheostomy with intermittent positive pressure ventilation, if laryngeal oedema is severe and patient shows signs of asphyxiation and hypoxaemia.
- Hypotension is managed with intravenous fluids and if required with dopamine.
- Bronchodilators—nebulised salbutamol.
- Glucagon for patients taking β-blockers.
- Hydrocortisone 200 mg IV stat (not effective for the acute event as it takes 4 hours to act; but may be considered for persistent bronchospasm and hypotension).
- Diphenhydramine (H_1 blocker), 50–80 mg IM/IV.
- Ranitidine (H_2 blocker), 50 mg IV.

Q. What is meant by serum sickness?

- This is a type III hypersensitivity immune reaction where IgG is produced in response to the injection of foreign antigen in large quantities. These form soluble immune complexes that result in fever, vasculitis, glomerulonephritis, arthritis and cardiac involvement. At the local site of injection, there would be urticaria and enlargement of lymph nodes. This is an immune complex deposition mediated disease.

Q. Write a short note on DRESS syndrome

- DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome is a potentially life-threatening adverse reaction to a number of drugs.
- Common causes include phenytoin, carbamazepine, sulphonamides and phenobarbital. Immunosuppression may predispose individuals to develop this condition, especially when accompanied by a primary or reactivation of human herpesvirus-6 infection.
- It presents as morbilliform cutaneous eruption with fever, lymphadenopathy, haematologic abnormalities and multiorgan manifestations (e.g. hepatic, renal, pulmonary, cardiac, neurologic, gastrointestinal and endocrine abnormalities). Fever generally precedes cutaneous eruptions by several days, with temperatures ranging from 38°C to 40°C and may last for several weeks.
- Occurs about 2 to 6 weeks after initiation of a drug.
- Atypical lymphocytosis. Leucocytosis occurs in 90% while eosinophilia in 50%.
- Mortality is about 10% and is usually due to fulminant hepatic failure.
- Treatment is supportive and use of corticosteroids

Q. Explain the HLA system.

- The HLA system plays a central role in intercellular recognition and discrimination between self and non-self.
- The term "tissue rejection" connotes a type IV immune reaction that leads to the destruction of a transplant by a recipient who is genetically non-identical to the donor. Here the recipient lymphoid system recognises foreign (non-self) antigens in the donor tissue. These cell surface antigens that evoke rejection of transplants are called human leucocyte antigen (HLA). The genes that code for HLA are called HLA genes or histocompatibility genes.
- The HLA genes are clustered and located on the short arm of chromosome 6, identified as HLA complex or the major histocompatibility complex (MHC). MHC is a general term used for all species.
- The HLA genes code for cell-surface glycoproteins called HLA or human leucocyte antigens.
- The HLA genes that are involved in the immune response fall into two main classes: class I and class II.

Class I Genes

- Three common class I genes are HLA-A, B and C. These genes produce class I molecules or antigens that are expressed by most somatic cells. Class I molecules interact with CD8+ T cells during antigen presentation and therefore, are involved in mainly driving cytotoxic reactions. Since this class of molecules is present on all nucleated cells, nearly all cells can present to cytotoxic cells.

Class II Genes

- Class II genes are HLA-D with several families (DR, DQ and DP are the major ones). These genes are expressed by a subgroup of immune cells known as APCs that include B cells, activated T cells, macrophages and dendritic cells. In the presence of IFN-γ, other cells can also express class II antigens. Class II antigens linked with CD4 molecules during antigen presentation and reaction induced by cells bearing this class of molecules is of helper type.

Other Genes

- Besides class I and class II genes, another group of genes, i.e. class III is present between class I and class II regions. Class III genes include genes for TNF-α, TNF-β, the complement components C2, C4 and Bf and the enzyme 21-hydroxylase. These are non-HLA genes.

HLA Genes and Immune Functions

- The main function of both the classes of genes is to present pathogen-derived peptides to T cells. The antigen must be presented to the T cells as a peptide fragment within the groove of the HLA molecules on the APCs. Free antigen will have no effect. Antigen expressed with class I is endogenous, i.e. the molecules are produced within the cell, such as viral proteins and tumour antigens. On the other hand, cells bearing class II molecules take up exogenous antigen by endocytosis and degrade it intracellularly. The processed antigen is then re-expressed on the cell surface with class II molecules.

Significance of HLA System

- HLA typing is prerequisite in selecting appropriate donor and recipient combinations for transplantation.
- Regulation of cell-to-cell interaction in the immune response (immune response Ir genes).
- Role in host defence against viral infections.
- Association of HLA with disease, e.g. individuals who possess HLA-B27 antigen have an 87-fold greater risk of developing ankylosing spondylitis than do individuals lacking this antigen. HLA genes are therefore related to disease susceptibility.

Q. What is acquired immunodeficiency syndrome (AIDS)? Discuss the staging, aetiology, transmission, clinical manifestations, laboratory diagnosis and management.

- Worldwide over 33 million individuals are seropositive for human immunodeficiency virus (HIV).
- In India, estimated number of HIV positive cases is 2.089 million . There has been an overall reduction of 57% in the annual new HIV infections among adult population from 2.74 lakh in 2000 to 1.16 lakh in 2011.
- Acquired immunodeficiency syndrome (AIDS) is caused by a single-stranded RNA human retrovirus known as human immunodeficiency virus. It possesses the RNA-dependent DNA polymerase [reverse transcriptase (RT) enzyme].

Definition and Staging

- An individual infected with HIV is known as HIV-infected individual.
- AIDS is defined as clinical diagnosis (presumptive or definitive) of any stage 4 condition (defined below) with confirmed HIV infection.

WHO Clinical Staging of HIV Infection

Clinical stage 1	Asymptomatic Persistent generalised lymphadenopathy
Clinical stage 2	Moderate unexplained weight loss (<10% of presumed or measured body weight) Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulceration Seborrhoeic dermatitis

Clinical stage 3	Fungal nail infections Unexplained severe weight loss (>10% of presumed or measured body weight) Unexplained chronic diarrhoea for longer than one month Unexplained persistent fever (above 37.6°C intermittent or constant for >1 month) Persistent oral candidiasis Oral hairy leucoplakia Pulmonary tuberculosis Severe bacterial infections Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis Unexplained anaemia (<8 g/dL), neutropenia (<500/μL) or chronic thrombocytopenia (<50,000/μL)
Clinical stage 4	HIV wasting syndrome *Pneumocystis* pneumonia Recurrent severe bacterial pneumonia Chronic herpes simplex infection Oesophageal candidiasis Extrapulmonary tuberculosis Kaposi's sarcoma Cytomegalovirus infection Central nervous system toxoplasmosis HIV encephalopathy Extrapulmonary cryptococcosis including meningitis Disseminated non-tuberculous mycobacterial infection Progressive multifocal leucoencephalopathy Chronic cryptosporidiosis (with diarrhoea) Chronic isosporiasis Disseminated mycosis (coccidiomycosis or histoplasmosis) Recurrent non-typhoidal Salmonella bacteraemia Lymphoma (cerebral or B-cell non-Hodgkin) or other solid HIV-associated tumours Invasive cervical carcinoma Atypical disseminated leishmaniasis

Aetiology

- Human retroviruses belong to two distinct groups: Human T lymphotropic viruses (HTLV-I and HTLV-II) and human immunodeficiency viruses (HIV-1 and HIV-2).
- HIV has an icosahedral structure containing numerous external spikes formed by two major envelope proteins, gp120 and gp41.
- HIV-1 comprises several subtypes with different geographic distribution.
- There are two groups of HIV-1: group M (major) and group O (outlier). The M group comprises nine subtypes or clades designated A, B, C, D, F, G, H, J and K as well as four major circulating recombinant forms (AE or simply E, AG, AGI and AB). Subtype C is the major clade of HIV in India.
- HIV RNA has three structural genes: *gag*, *pol* and *env*.
  - The *gag* gene encodes the structural proteins of the core (p24, etc.).
  - The *env* gene encodes the viral envelope glycoproteins, gp120 and gp41.
  - The *pol* gene encodes for enzymes crucial for viral replication. These are the RT that converts viral RNA into DNA, the integrase that incorporates the viral DNA into host chromosomal DNA and the protease that cleaves large Gag and Pol protein precursors into their components.

Replication Cycle of HIV

- HIV can infect a number of different cells, including CD4-bearing macrophages, T-helper lymphocytes and dendritic cells within the host.
- HIV attaches to the target cells through binding of surface glycoprotein gp120 to cell surface CD4 molecules.
- Binding to another co-receptor, CCR5 or CXCR4, produces conformational changes on viral surface exposing gp41 that allows it to fuse with the cell membrane. Inhibition of this binding, will inhibit viral replication.
- T-cell tropic HIV strains mainly use CXCR4 as a co-receptor and are called X4 strains, whereas macrophage-tropic strains responsible for host-to-host transmission, use CCR5 as a co-receptor and are referred to as R5 strains. The significant role

of CCR5 in this process is borne out by the observation that individuals homozygous for mutations within CCR5 gene are resistant to infection by HIV1.

- After the virus invades a macrophage or T lymphocyte, RT enzyme initiates copying of the viral RNA into single-stranded DNA and then a complimentary copy of DNA is created producing a double-stranded DNA.
- The viral DNA migrates and enters the host cell nucleus and becomes integrated into the cell DNA with the help of the enzyme integrase. The provirus can then remain latent or be active, generating products for the generation of new virions.
- Transcription and translation of viral DNA produces viral RNA. The HIV genes, *gag* and *pol*, produce large polypeptides. Before budding of virus, these polypeptides undergo processing by the enzyme protease.
- Once infection is systemic, HIV preferentially targets CCR5/CD4 memory T lymphocytes in the gastrointestinal tract, a crucial element in host defence in the gut.
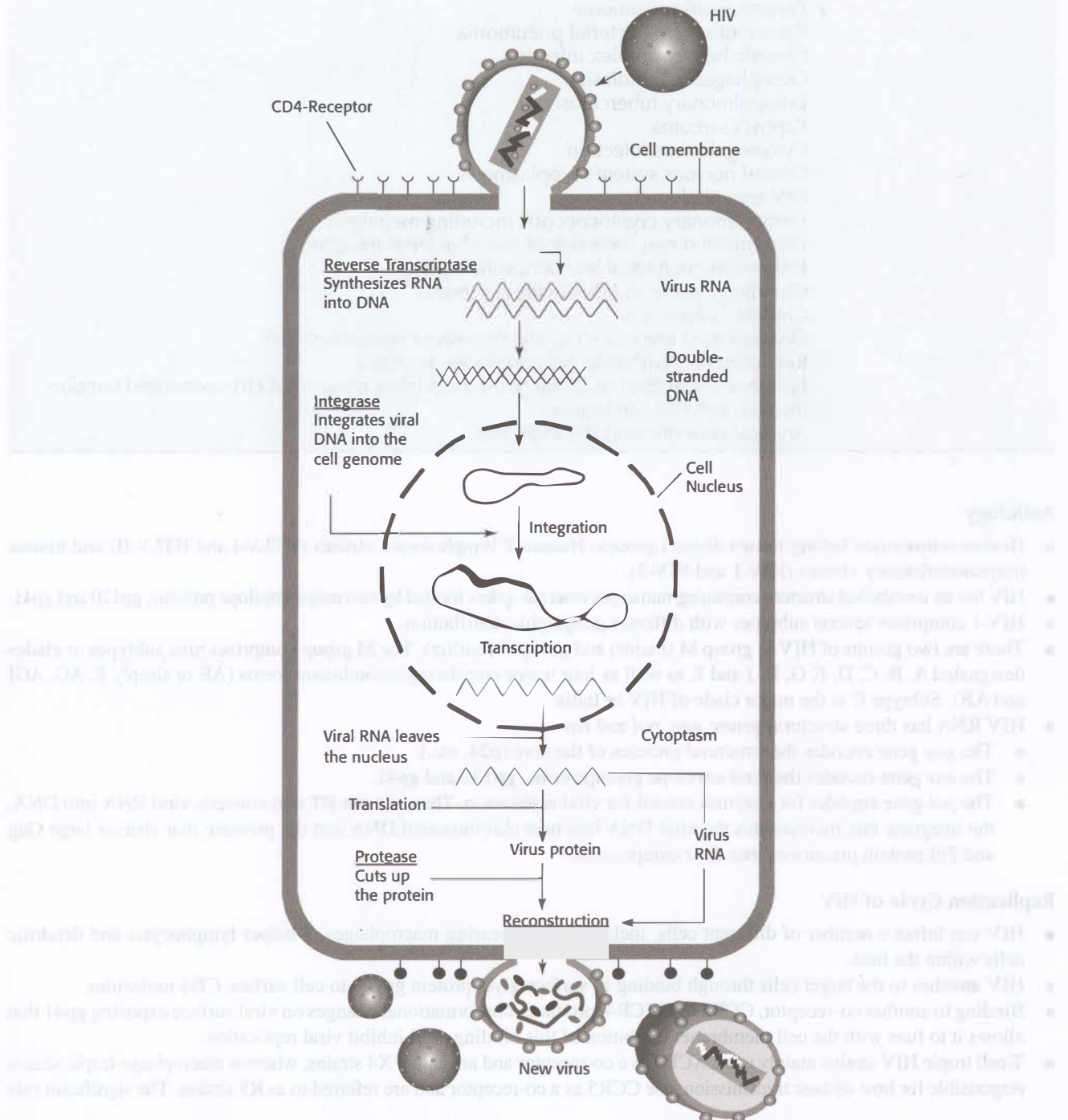
Transmission

Routes of Transmission of HIV

Parenteral	Sexual
• Transfusion of blood and blood products	• Homosexuals
• Needle sharing (including intravenous drug users)	• Heterosexuals
• Needle stick injuries	**Perinatal**
• Injections with unsterile needles	• Vertical transmission from mother to foetus
• Splash of body fluids on mucosa (mouth, nose and eyes)	• Peripartum
	• Breast feeding

Routes not Involved in Transmission of HIV

- Close personal contact including kissing
- Household contact
- Contact at school, swimming pool
- Sharing of utensils and insect bites

Clinical Manifestations of HIV/AIDS

- The seroconversion occurs within 3 weeks to 3 months after exposure.

Spectrum of HIV Infection/AIDS

- Acute seroconversion illness
- Asymptomatic viral carriage (with or without abnormal cell-mediated immunity)
- Persistent generalised lymphadenopathy
- AIDS-related complex (also known as HIV-associated neurocognitive disorders—HANDs), and HIV constitutional disease
- Opportunistic infections
- Malignancies

Acute Seroconversion

- In about 15% of cases acquiring HIV infection, an acute viral illness develops about 6 weeks after exposure.

Clinical and Laboratory Features

Clinical features	Laboratory features
• Fever	• Thrombocytopenia
• Fatigue	• Elevated liver enzymes
• Pharyngitis	
• Headache	
• Myalgia/arthralgia	
• Urticaria, skin rash	
• Lymphadenopathy	
• Aseptic meningitis, encephalitis, cranial nerve palsies	

- This illness is self-limiting and lasts for 2–3 weeks.
- Usually, the person is in the "window period" and hence seronegative but during the recovery phase HIV antibody test often turns positive.

- When diagnosis is not made in acute phase it is often delayed for years until opportunistic infections develop.
- Diagnosis can be made by nucleic acid amplification tests that detect viral genetic material from patient specimens. Another method is to detect p24 antigen.
- Whether ART is required at this stage is not clear. Current guidelines recommend initiating ART at this time to preserve immune function and reduce infectiousness; however, clinicians should assess patient's readiness, including adherence, prior to initiating therapy.

Asymptomatic Carrier Stage

- The individual is asymptomatic but is potentially infectious for others.
- This stage may last for 5–10 years.
- Laboratory abnormalities may include anaemia, leucopenia, lymphopenia, reduced CD4+ counts and cutaneous anergy.

Persistent Generalised Lymphadenopathy (PGL)

- Though asymptomatic, some HIV carriers develop PGL.
- It is characterised by lymph node enlargement at two or more extrainguinal sites that are non-contiguous that persist for more than 3 months in the absence of any other illness. The lymph nodes are more than 1 cm in size.
- Biopsy reveals non-specific lymphoid hyperplasia.

HIV Constitutional Disease and AIDS-Related Complex (ARC)

- Within an average of 7–8 years, sometimes earlier (particularly in children), the patients develop severe diarrhoea, night sweats, fever and weight loss. This is known as ARC and it heralds the onset of terminal phase of HIV infection.
- ARC is diagnosed in a patient who has at least two of the following clinical symptoms and signs along with two or more abnormal laboratory features that persist for more than 3 months:
  - Fever more than 38°C (intermittent or continuous).
  - Weight loss of more than 10% of body weight.
  - PGL.
  - Diarrhoea.
  - Fatigue and night sweats.
  - Lymphopenia, leucopenia and thrombocytopenia.
  - Reduced helper cells.
  - Cutaneous anergy.
- The condition of ARC with minor opportunistic infections like oral candidiasis is known as constitutional disease.

Full-Blown AIDS

- Within a few months of showing features of ARC, the CD4+ count drops below 500/mm^3 and the patient develops a number of life-threatening infections and cancers. The patient may also develop several neurological features. Clinical features of full-blown AIDS can be categorised into certain well-defined patterns (described below).

List of Important Infections and Cancers in AIDS

Infections	Cancers
• *Pneumocystis jirovecii* • *Candida* • *Cryptococcus* • *Toxoplasma* • Typical/atypical mycobacteria • Amoebiasis	• Kaposi's sarcoma • B-cell lymphoma of brain • Others

Relation between CD4+ Cell Count and Common Illnesses in HIV Patients

CD4+ count	Illnesses
• 200–350/μL	• Herpes simplex • Tuberculosis • Oral and vaginal thrush • Herpes zoster
• 100–200/μL	• *Pneumocystis jiroveci* pneumonia • *Candida* oesophagitis
• 50–100/μL	• Cryptococcal meningitis • AIDS dementia • Toxoplasma encephalitis
• <50/μL	• Progressive multifocal leucoencephalopathy • *Mycobacterium avium* complex • Cytomegalovirus infection

Pulmonary Diseases

- In a patient with AIDS, three common causes of lung involvement are tuberculosis, bacterial pneumonia and *Pneumocystis jirovecii* pneumonia (PCP). Other causes of lung involvement include CMV, toxoplasma and fungal infections, and Kaposi's sarcoma.
- Tuberculosis generally involves lower lobes of the lungs and cavitation is uncommon.
- Presentation of bacterial pneumonia is similar to that in immunocompetent people.

Pneumocystis jiroveci Infection

- *Pneumocystis jiroveci* (previously known as *Pneumocystis carinii*) is a fungus.
- Three stages in life cycle: cysts, trophozoites (outside cyst) and sporozoites (inside cyst). Methenamine silver stains the cyst wall while Giemsa stain is taken by the wall of the trophozoites and sporozoites. Trophozoites are in plenty in the lungs.

Clinical Features

- PCP (Pneumocystis pneumonia) presents with subacute onset of progressive dyspnoea, fever and non-productive cough that gradually lead to respiratory distress and cyanosis. Acute onset is uncommon. Examination reveals crepitations; findings of consolidation are unusual.
- Extrapulmonary sites may be involved which include skin, meninges, brain, eyes, heart, liver, spleen and kidneys.

Diagnosis

- Arterial blood gas:
  - In mild cases, room air arterial oxygen (pO$_2$) >70 mmHg or alveolar-arterial O$_2$ difference <35 mmHg.
  - In moderate to severe cases, pO$_2$ <70 mmHg or alveolar–arterial O$_2$ difference >35 mmHg.
- Chest radiograph shows a ground glass appearance or bilateral infiltrates but in some patients it may be normal.
- Unusual patterns on X-ray include nodular shadows, cystic lesions, pneumothorax, lobar consolidation and apical involvement (in patients on pentamidine prophylaxis). Pleural effusion, cavitation and mediastinal lymphadenopathy are rare.
- Serum shows elevated LDH levels.
- Pulmonary functions show restrictive pattern with reduced diffusion capacity.
- CT chest shows patchy ground glass appearance.
- Gallium-67 scan shows diffuse pickup even when the radiograph is normal.
- Diagnosis is established by sputum examination (spontaneously expectorated or induced by hypertonic saline nebulisation). Other modes include bronchial lavage and transbronchial biopsy.

Management

- The drug of choice is trimethoprim/sulphamethoxazole combination for 21 days.

Mild cases	Moderate to severe cases (PaO$_2$ <70 mmHg)
• Trimethoprim 5 mg/kg 6 hourly + sulphamethoxazole 25 mg/kg 6 hourly orally OR • Trimethoprim 5 mg/kg 6 hourly + dapsone 2 mg/day OR • Pentamidine 4 mg/kg/day IV OR • Atovaquone 750 mg tid	• Trimethoprim 5 mg/kg 6 hourly + sulphamethoxazole 25 mg/kg 6 hourly IV OR • Pentamidine 4 mg/kg/day IV OR • Clindamycin (600 mg qid) + primaquine (30 mg od) • In all cases, add prednisolone 40 mg bid for 5 days, then 40 mg/day for 5 days and then 20 mg/day for 11 days

Prophylaxis

- Primary prophylaxis is indicated in patients with CD4 cell count <200/mm^3 or if there is a history of oropharyngeal candidiasis. Secondary prophylaxis is indicated in all patients who have recovered from PCP.
  - Trimethoprim 160 mg + sulphamethoxazole 800 mg/day, i.e. one single-strength tablet daily (TMP–SMX at a dose of one double-strength tablet daily confers cross-protection against toxoplasmosis also) OR
  - Aerosolised pentamidine 300 mg once a month OR
  - Dapsone 50 mg bid.
  - Others include atovaquone (1500 mg od), or dapsone (200 mg) plus pyrimethamine (75 mg) plus leucovorin (25 mg) all once a week.

Gastrointestinal Diseases

Causes of Diarrhoea

Infections	HIV related
• *Salmonella* • *Shigella* • *Campylobacter* • *Escherichia coli* • *Cryptosporidium* • *Giardia* • *Isospora* • *Microsporidium* • *Entamoeba histolytica* • CMV • *Mycobacterium avium* complex	• HIV invading gut epithelium **GI malignancies** • Lymphoma • Kaposi's sarcoma

- Acute infection with various bacterial agents usually produces abdominal pain, fever, diarrhoea and bloody stools.
- Standard antibiotic therapy is recommended; however, patients with AIDS are more likely to have protracted illness and suffer recurrences.
- Protozoal, CMV and mycobacterial infections tend to produce protracted diarrhoea and fluid and electrolyte imbalance.
- ART is indicated in all patients with opportunistic infections including cryptosporidium, microsporidium and isospora infections as immune restoration often leads to eradication of infections. Nitazoxanide is the treatment of choice for *Cryptosporidium* infection. TMP–SMX is the antimicrobial agent of choice for treatment of isosporiasis.

Oesophagitis

- Oesophagitis is encountered in as many as 90% of the patients with AIDS. It is usually due to *Candida*, CMV and *Herpes simplex* virus.

Mucocutaneous Diseases

- These include candidiasis, warts, molluscum contagiosum, herpes simplex, varicella-zoster and Kaposi's sarcoma.
- Kaposi's sarcoma presents as red or purple, flat or raised skin lesions. Involvement of lymph nodes, oral mucosa and viscera is quite common.

Neurological Diseases

Acute Meningitis

- During acute seroconversion, CNS invasion occurs in more than 90% cases. The clinical spectrum varies from a silent CSF pleocytosis, aseptic meningitis, an infectious mononucleosis-like syndrome, multiple cranial nerve palsies to acute encephalopathy. CSF shows lymphocytosis along with raised proteins (<200 mg/dL). CT is normal and recovery is usually complete.

AIDS Dementia Complex (ADC) or HIV-Associated Neurocognitive Disorders (HANDs)

- It precedes the diagnosis of AIDS in about 25% of cases and can occur at any stage of AIDS.
- Includes three categories: asymptomatic neurocognitive impairment, mild neurocognitive disorder (MND), and HIV-associated dementia (HAD).

Vacuolar Myelopathy

- It involves the white matter of lateral and posterior columns of the spinal cord resulting in spastic paraparesis and sensory ataxia. The onset is subacute.

Viral Infections

- Progressive multifocal leucoencephalopathy (PML) is caused by the polyoma virus [JC virus (JCV)] and is characterized by focal neurological abnormalities including blindness, aphasia, hemiparesis and ataxia that progress to altered sensorium and death within 6 months. Focal or multifocal nature of PML is responsible for distinct focal symptoms and signs rather than a more diffuse encephalopathy or dementia. CT scan shows non-enhancing, focal hypodense lesions. MRI confirms distinct white matter lesions in areas of the brain corresponding to clinical deficits. Confirmation is by PCR to identify JCV DNA in CSF. Treatment is mainly by starting ART.
- Herpes simplex encephalitis may have an insidious onset as compared to an immunocompetent host. Despite treatment with acyclovir the prognosis is poor.
- Herpes zoster may also produce myelitis or radiculitis.
- Cytomegalovirus may present with slowly progressive encephalitis or with myelitis and retinitis (retinal haemorrhage resulting in blindness). Other features include colitis and oesophagitis. Treatment involves lifelong use of intravenous ganciclovir (or oral valganciclovir) and foscarnet, either alone or in combination. For CMV retinitis, ganciclovir intraocular implant plus oral valganciclovir is superior to once daily IV ganciclovir.

Fungal Infections

- Cryptococcal meningitis may present with headache and fever. However, meningismus may be present in only a minority of cases and fever may be absent in 10–30% of episodes. The CSF may not show pleocytosis or raised proteins in some cases, thus complicating the diagnosis. However, cryptococcal antigen and culture are usually positive, both in serum and CSF. India ink staining on CSF may show the organisms. Treatment is by administering amphotericin B (0.7 mg/kg/day) and flucytosine (25 mg/kg QID) for 2 weeks followed by fluconazole (400 mg/day) for 8–10 weeks. Relapse rates are high and therefore, continuous therapy with fluconazole (200 mg/day) is recommended for at least one year to prevent relapse.

Bacterial Infections

- Tuberculous meningitis, common in AIDS patients, may present in a manner similar to cryptococcal meningitis. CSF usually reveals elevated cell counts and protein along with low glucose. CT scan may show multiple ring lesions suggestive of tuberculomas.
- Syphilis may progress rapidly to late manifestations including neurosyphilis. Manifestations include optic neuritis, uveitis, meningitis, encephalitis and cerebral infarction.

Protozoan Infections

- The most common opportunistic infection of CNS is caused by *Toxoplasma gondii*. Toxoplasma encephalitis presents with headache, confusion, seizures, ataxia and focal deficits. A contrast CT scan is required for making a presumptive diagnosis of toxoplasma infection as the lesions appear as single or multiple contrast enhancing lesions often with surrounding hypodensity due to oedema. Patients are seropositive for antitoxoplasma

IgG antibodies. Treatment is by a combination of pyrimethamine + sulphadiazine + leucovorin for at least 6 weeks.

Prophylaxis

- Prophylaxis indicated in toxoplasma-seropositive patients with a CD4+ count <100 cells/μL. One double-strength tablet of TMP–SMX daily is the preferred regimen.
- If patients cannot tolerate TMP–SMX, alternative is dapsone + pyrimethamine + leucovorin.

Miscellaneous CNS Manifestations

- Primary CNS lymphoma occurs in about 5% of cases and may present with encephalopathy, focal deficits, seizures or lymphomatous meningitis. CT scan shows multiple hypodense lesions with homogeneous or ring enhancement.
- Polyneuropathy.

Ocular Diseases

- Cotton wool spots are seen in 40–60% of patients with AIDS and are benign in nature.
- Retinitis due to CMV is the most serious infection of the eyes. This may lead to a painless visual loss. Fundus may reveal cotton wool spots similar in appearance to the benign spots. More commonly, there are fluffy white retinal lesions with areas of haemorrhage. CMV can also produce colitis and oesophagitis.
- Another cause of retinitis in AIDS patients is infection with toxoplasma that presents with visual loss, photophobia and floaters.
- Herpes zoster may lead to ocular pain, conjunctival injection and corneal opacification.

Others

Mycobacterium avium Complex (MAC)

- Usually occurs if CD4+ <50/μL.
- Often presents with disseminated multiorgan infection (hepatomegaly, splenomegaly, lymphadenopathy) along with fever, night sweats, weight loss, fatigue, diarrhoea and abdominal pain.
- Localised manifestations occur among persons who are receiving and have responded to HAART. Localised syndromes include cervical or mesenteric lymphadenitis, pneumonitis, pericarditis, osteomyelitis, skin or soft tissue abscesses, genital ulcers or CNS infection.
- Anaemia and raised alkaline phosphatase are common.
- Blood, bone marrow or lymph node aspirate may grow the organisms.
- Chemoprophylaxis against disseminated MAC disease is indicated if CD4+ count <50/μL. Azithromycin or clarithromycin are the preferred prophylactic agents.
- Treatment includes use of clarithromycin + ethambutol + rifabutin.

Cardiovascular Diseases

- Increased risk for cardiovascular (CV) diseases (e.g. coronary artery disease, cardiomyopathy, myocarditis, arrhythmias, etc.).
- Increased risk of CAD and CHF due to several factors:

- Traditional risk factors (e.g. hypercholesterolaemia/atherogenic dyslipidaemia, high blood pressure, smoking, proatherogenic diet, obesity, diabetes, low physical activity).
- Decreased apolipoprotein B
- Increased level of proatherogenic 'small dense LDL'
- Increased LDL cholesterol, particularly small dense LDL during treatment.
- Hypertriglyceridaemia due to PI drugs
- Increaesd blood pressure and insulin resistance due to HAART
- Elevated inflammatory parameters (e,g, D-dimer, interleukin-6, C-reactive protein)
- Direct damage to coronary arterial wall by HIV

- Myocarditis may be due to infections (e.g. fungal—Candida, Histoplasma, Cryptococcus, Aspergillus; viral—Herpes simplex, Cytomegalovirus; bacterial—tuberculosis, toxoplasmosis; and HIV infection itself)

Laboratory Diagnosis of HIV Infection

- Antibodies against the virus are detectable within 3–12 weeks after infection. Most commonly, enzyme-linked immunosorbent assay (ELISA) is employed for screening while confirmation is done by western blot test.
- Other findings include lymphopenia, leucopenia, thrombocytopenia and decrease in T4-helper cells (CD4+ counts).
- Other tests include antigen detection (p24 assays) and polymerase chain reaction (PCR) for measuring the amount of viral particles (HIV RNA) in the blood (viral load).
- Specific investigations will be required depending upon the presentation of the patient.

Management of a Patient with HIV Infection

General Measures

- These include balanced diet, quitting smoking and intake of alcohol, adequate rest and practice of safer sex so as to avoid infection of partner and also to avoid infection with other organisms that may hasten the progress of the disease.
- An important aspect of treatment is counselling and proper education of the patient.

Treatment of Common Opportunistic Infections in AIDS

Opportunistic infection	First-line treatment	Alternate treatment
Pneumocystis jirovecii	See text	See text
Toxoplasma	Pyrimethamine 50–100 mg/day + Sulphadiazine 2 g QID	Pyrimethamine 50–100 mg/day + Clindamycin 500 mg QID
Cryptococcus	Amphotericin 0.3 mg/kg/day + Flucytosine 25–37 mg/kg QID	Amphotericin 0.7 mg/kg/day
Isospora belli	Co-trimoxazole 7 mg/kg	–
Candida (mucosal)	Clotrimazole 200–600 mg OR Fluconazole 50–100 mg/day	Ketoconazole 200 mg/day
Candida (systemic)	Amphotericin 0.3 mg/kg/day	–
Cytomegalovirus	Ganciclovir 5 mg/kg BID IV	Foscarnet 60 mg/kg TID
H. simplex (oral)	Acyclovir 200–400 mg five times/day	Valacyclovir 1 g BID
H. simplex (encephalitis)	Acyclovir 10 mg/kg TID IV	–
Herpes zoster (local)	Valacyclovir 1 g BID or Famciclovir 500 mg TID	Acyclovir 30 mg/kg/day in five doses
Herpes zoster (disseminated)	Acyclovir 10 mg/kg TID	

Antiretroviral Drugs

- Based on the action at various sites during HIV replication cycle and structure of drugs, following classes of drugs are presently available for treatment of HIV infection.

Nucleoside reverse transcriptase inhibitors (NRTIs)	Fusion inhibitors

Nucleoside reverse transcriptase inhibitors (NRTIs)
- Zidovudine (AZT, ZDV)
- Didanosine (ddI)
- Zalcitabine (ddC)
- Stavudine (d4T)
- Lamivudine (3TC)
- Abacavir (ABC)
- Emtricitabine (FTC)

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Nevirapine (NVP)
- Delavirdine (DLV)
- Efavirenz (EFV)
- Etravirine (ETR)
- Rilpivirine (RPV)

Nucleotide reverse transcriptase inhibitor (nRTI)
- Tenofovir disoproxil fumarate (TDF)

Fusion inhibitors
- Enfuvirtide (eT20)

Protease inhibitors (PIs)
- Indinavir (IDV)
- Ritonavir (RTV)
- Saquinavir (SQV)
- Nelfinavir (NFV)
- Amprenavir (APV)
- Lopinavir/ritonavir (LPV/RTV)
- Atazanavir (ATV)
- Fosamprenavir (FOSAPV)
- Tipranavir (TPV)
- Darunavir (TMC114)

Integrase strand transfer inhibitors (INSTIs)
- Raltegravir (RAL)
- Dolutegravir (DTG)
- Elvitegravir (EVG)

CCR5 inhibitors
- Maraviroc (MVC)

Note: Lamivudine, emtricitabine and tenofovir also have activity against hepatitis B virus

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

- Mechanism of action: These agents diffuse into the infected cells and are converted to their active triphosphate forms by cellular kinases. These active nucleosides are incorporated into the growing viral DNA and cause premature chain termination.
- Fatty change in the liver (hepatic steatosis) and lactic acidosis are two important adverse effects of NRTIs that occur due to their effect on cellular mitochondria.
- Zidovudine can produce neutropenia and anaemia.
- Zalcitabine and stavudine may produce peripheral neuropathy.
- Didanosine may lead to pancreatitis.
- Zidovudine and stavudine can produce lipoatrophy.
- Zidovudine should not be combined with stavudine.
- Abacavir can cause an increased risk of cardiovascular events and is associated with a serious hypersensitivity reaction in patients who are HLA-B*5701 positive.

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

- Mechanism of action: NNRTIs bind directly to the RT enzyme causing inhibition of its function.
- Members of this class are highly active against HIV-1 but not HIV-2.
- Nevirapine may produce skin rash and hepatitis.
- Efavirenz should be avoided in first trimester of pregnancy. It causes CNS toxicity (dizziness, insomnia, impaired concentration, agitation, amnesia, somnolence, abnormal dreams, hallucinations and suicidal tendencies).

Nucleotide Reverse Transcriptase Inhibitors (nRTIs)

- This category includes nucleotide analogues that inhibit reverse transcriptase inhibitor.
- At present, only tenofovir disoproxil fumarate is approved for use.
- Tenofovir can cause renal toxic effects and osteopenia.

Fusion Inhibitors

- This group contains agents that block the initial fusion of HIV with cell-surface receptors.
- Enfuvirtide (T20) is being used from this class of drugs. It is given by subcutaneous route. It does not inhibit HIV-2.

Protease Inhibitors (PIs)

- Mechanism of action: These drugs inhibit enzyme protease and therefore, inhibit the final assembly of virus before release from infected cells.

- PIs have been associated with body fat redistribution that manifests physically as thinning of arms, legs and face and/or deposition of fat in the abdominal and shoulder regions along with lipomas (lipodystrophy). It occurs in 6–80% of patients and develops after several months of therapy. The effects on fat metabolism may lead to raised levels of serum cholesterol and triglycerides, insulin resistance and rarely elevated blood glucose levels, which may increase cardiovascular risk.
- Some PIs, especially indinavir may produce hyperglycaemia.
- PIs have several drug interactions that need to be kept in mind while prescribing other drugs to patients taking PIs.
- Ritonavir is a potent inhibitor of the P450CYP3A enzyme and is typically used at low doses to boost the concentrations of other protease inhibitors since most are heavily metabolised by the P450 system. Hence PIs are often used in combination with ritonavir ("ritonavir boosting").

CCR5 Inhibitors

- Maraviroc is a CCR5 inhibitor that binds to the host cells through CCR5 receptors. It is only active in patients who do not have virions that use CXCR4 for cell entry. A specialised assay is therefore needed to screen for co-receptor tropism which will determine if a patient's virus will respond to this medication.

Intergrase Strand Transfer Inhibitors (INSTIs)

- Three INSTIs, raltegravir, dolutegravir and elvitegravir are in use.
- They inhibit action of integrase which is required for insertion of viral genome into the DNA of the host cell. Since integration is a vital step in retroviral replication, inhibiting it can stop further progression of disease.
- These drugs are generally well tolerated.

Recommendations on the Use of Antiretroviral Agents

- It must be understood that eradication of HIV infection cannot be achieved with the currently available antiretroviral regimens. This is due to the establishment of a pool of latently infected CD4+ cells during the earliest stages of acute HIV infection that persists with an extremely long half-life.
- The use of highly active antiretroviral therapy (HAART) has been successful in reducing morbidity in HIV patients and improving the quality of life.
- The term HAART indicates use of combinations of drugs so as to achieve the goals of maximal and durable suppression of viral load, restoration and preservation of immune function, improvement of quality of life and reduction of HIV-related mortality and morbidity.

Indications for Antiretroviral Therapy

- Antiretroviral treatment is now recommended for all patients with HIV, particularly those with CD4+ <500/mm³.
- ART is also recommended for serodiscordant couples, pregnant women living with HIV, people with TB and HIV, people with HIV and chronic hepatitis B or hepatitis C and children living with HIV who are younger than five years, irrespective of CD4 cell count.

Evaluation before Initiating HAART

- Complete history and physical examination.
- Ophthalmologic examination.
- Complete blood count, blood sugar, chemistry profile, urine analysis, creatinine clearance and lipid profile.
- CD4+ cell count and percentage. Measurement of CD8 cell count is unnecessary.
- Quantitative plasma HIV RNA.
- Drug resistance with an HIV genotype test strongly recommended because drug-resistant virus can be transmitted from one person to another
- Coreceptor tropism testing if use of a CCR5 antagonist is being considered.
- HLA-B*5701 testing before initiating abacavir therapy as patients positive for this HLA type are prone to develop severe hypersensitivity reaction.
- Others tests including VDRL, Mantoux test, toxoplasma IgG serology, chest radiography and serology for hepatitis C and B.

Antiretroviral Regimens

- Most commonly used regimens include a PI with two NRTIs, or one NNRTI with two NRTIs or three NRTIs.
- While initiating therapy one should begin with an effective regimen. Consideration should also be given to the number of pills per day, frequency of dosing, food requirements, toxicity and drug interactions with other drugs being used by the patient.
- When starting ART, all drugs should be started simultaneously at full dose with the exception of ritonavir and nevirapine where dose escalation is recommended.

Initial Treatment of HIV Patients

Recommended initial ART regimens for all patients:

Non-nucleoside reverse transcriptase inhibitor-based regimen:
- Efavirenz + Tenofovir + Emtricitabine (or Lamivudine)

Protease inhibitor-based regimens:
- Atazanavir/ritonavir + Tenofovir + Emtricitabine (or Lamivudine)
- Darunavir/ritonavir + Tenofovir + Emtricitabine (or Lamivudine)

Integrase inhibitor-based regimens:
- Dolutegravir + Abacavir + Lamivudine (or Emtricitabine) only for patients who are HLA-B*5701 negative
- Dolutegravir + Tenofovir + Eemtricitabine (or Lamivudine)
- Raltegravir + Tenofovir + Emtricitabine (or Lamivudine)

Alternative regimens for patients with plasma HIV RNA <100,000 copies/mL (in addition to above-mentioned regimens):

Non-nucleoside reverse transcriptase inhibitor-based regimen:
- Efavirenz + Abacavir + Lamivudine (or Emtricitabine) only for patients who are HLA-B*5701 negative
- Rilpivirine + Tenofovir + Emtricitabine (or Lamivudine) only for patients with CD4 count >200 cells/mm^3

Protease inhibitor-based regimens:
- Atazanavir/ritonavir + Abacavir + Lamivudine (or Emtricitabine) only for patients who are HLA-B*5701 negative

Alternative initial regimens (robust data not available or have disadvantages compared to recommended initial regimens):

Non-nucleoside reverse transcriptase inhibitor-based regimen:
Zidovudine + Lamivudine + Efavirenz
Zidovudine + Lamivudine + Nevirapine
Tenofovir + Nevirapine + Lamivudine (or Emtricitabine)

Protease inhibitor-based regimens:
- Darunavir/ritonavir + Abacavir + Lamivudine (or Emtricitabine) only for patients who are HLA-B*5701 negative
- Lopinavir/ritonavir + Abacavir + Lamivudine (or Emtricitabine) only for patients who are HLA-B*5701 negative
- Lopinavir/ritonavir + Tenofovir + Emtricitabine

Integrase inhibitor-based regimens:
- Raltegravir + Abacavir + Lamivudine (or Emtricitabine) only for patients who are HLA-B*5701 negative

Note: National AIDS Control Organization still recommends use of Lamivudine + Zidovudine or Tenofovir + Nevirapine or Efavirenz (Efavirenz if patient is on ATT) because of cost-effectiveness.

Combinations/Drugs not Recommended as Initial Treatment (Due to Inferior Efficacy or Increased Toxicity Compared to Recommended Regimens)

Combinations	Drugs
• Stavudine + Zidovudine	• Delavirdine
• Stavudine + Lamivudine	• Nevirapine
• Stavudine + Didanosine	• Nelfinavir
• Zalcitabine + Didanosine	• Darunavir (unboosted)
• Zalcitabine + Lamivudine	• Fosamprenavir (boosted or unboosted)
• Zalcitabine + Stavudine	• Indinavir (boosted or unboosted)
• Zalcitabine + Zidovudine	• Ritonavir (as sole PI)
• Didanosine + Tenofovir	• Saquinavir (boosted or unboosted)
• Didanosine + Lamivudine	• Saquinavir (hard gel capsules)
• Abacavir + Zidovudine + Lamivudine	• Maraviroc
• Abacavir + Zidovudine + Lamivudine + Tenofovir	

Factors Affecting Response to HAART

- To maximise the benefits of ART following factors should be ensured:
  - Adherence to the drug regimen.
  - Adequate serum levels of antiretroviral drugs.
  - Rational sequencing of antiretroviral drugs to preserve future treatment options for as long as possible.

Monitoring of Therapy

- After initiation of ART, HIV RNA should be measured at 4–8 weeks to assess the efficacy of treatment as there should be a large decline in viral load during this period. The viral load should continue to decline after that and by 16–20 weeks it should be undetectable (i.e. <50 RNA copies/mL).
- A significant increase in CD4+ cell count is an increase of >30% from baseline for absolute cell numbers within 3–6 months.

Q. Discuss tuberculosis in HIV infection.

Q. Describe HAART and antitubercular drugs.

- Leading cause of morbidity and mortality in HIV infection.
- 25–65% persons with HIV infection have tuberculosis.
- Estimated annual risk of reactivation among those co-infected with HIV and TB is about 5–8% with a cumulative lifetime risk of 30% or more compared to a cumulative lifetime risk of 5–10% in HIV-negative adult patients.
- Course of HIV infection is accelerated subsequent to the development of TB.
- Prevalence of multidrug resistant TB is higher in HIV-positive compared to HIV-negative persons. However, this is not caused directly by HIV infection.

Clinical Features

- Active TB occurs throughout the course of HIV disease.
- Clinical presentation of TB in HIV-infected persons depends on the level of immunosuppression resulting from HIV infection. In patients with relatively intact immune function (CD4+ count >200/mm^3) pulmonary TB is more frequently seen than extrapulmonary TB. Chest radiographic findings include upper lobe infiltrates and cavitation, similar to those in HIV-negative individuals with pulmonary tuberculosis. Sputum smears are often positive for acid-fast bacilli.
- As immunosuppression progresses, extrapulmonary tuberculosis becomes increasingly common. The disease is often disseminated.

Diagnosis

- Please see topics of pulmonary and extra-pulmonary tuberculosis
- Screening for HIV in those with possible TB.
- There has been a switch from voluntary counseling and testing (VCT) to provider-initiated testing and counseling (PITC) in patients with diagnosed tuberculosis. With PITC, all patients undergo routine testing unless they specifically opt out.
- Another change has been to expand PITC to include all patients being investigated for TB regardless of whether or not TB is diagnosed.

Treatment Considerations

- Incidence of relapse and/or failure among patients treated with intermittent TB therapy throughout was two to three times higher than that in patients who received a daily intensive phase. Hence, daily therapy with antitubercular drugs is recommended in HIV-positive patients.
- Protease inhibitors (PIs) and NNRTIs are antiretroviral agents that may inhibit or induce cytochrome P-450 isoenzymes (CYP450). Rifampicin induces CYP450 and may substantially decrease blood levels of the antiretroviral drugs.
- NRTIs are not metabolised by CYP450. Concurrent use of NRTIs and rifampicin is not contraindicated and does not require dose adjustments.
- Rifampicin can be used for the treatment of active TB in patients on NNRTI efavirenz and two NRTIs.It should not be used in patients on PIs.

- Rifabutin is preferred over rifampicin due to lesser degree of drug interactions with PIs. It may be used in a dose of 300 mg/day in patients on NRTIs and NVP. However, its dose should be reduced to 150 mg per day when it is administered to patients taking ritonavir or ritonavir/ lopinavir. On the other hand, its dose should be increased to 450-600 mg daily when it is used concurrently with efavirenz.
- Simultaneous initiation of treatment for tuberculosis and HIV should be avoided:
  - If CD4+ counts are <50/mm^3, HAART should be started within 2 weeks of TB treatment.
  - If CD4 counts ≥50 cells/mm^3 with patient having severe disease (as indicated by clinical evaluation including low body mass index, low haemoglobin, low albumin, organ system dysfunction, or extent of disease), HAART should be initiated within 2 to 4 weeks of starting TB treatment
  - If CD4 counts ≥50 cells/mm^3 with patient not having severe disease, HAART may be initiated after 8 weeks of TB treatment. This is to reduce confusion about overlapping toxicities, drug interactions and occurrence of paradoxical reactions or IRIS.

Q. Describe the management of HIV/AIDS during pregnancy.

- There are currently limited data available on the safety of antiretroviral agents during pregnancy. In general, ART in pregnant females should not be withheld unless the risk of adverse effects outweighs the possible benefits. When ART is given during pregnancy, zidovudine should be included wherever possible. Regardless of the antepartum ART, intravenous ZDV during labour and oral ZDV to the newborn is recommended to prevent perinatal transmission of HIV.
- Efavirenz should be avoided in the first trimester.
- If the mother cannot afford drugs, cannot tolerate triple-drug regimens or does not want to take the possible risks to the baby, antiretroviral prophylaxis should be offered to reduce the chances of perinatal transmission (previously known as mother-to-child transmission or MTCT). For this, oral ZDV throughout antenatal period (at least from 28 weeks onwards), intravenous ZDV during intranatal period and oral ZDV to the newborn should be given for 6 weeks.
- If mother is found to be HIV positive at the time of labour, intravenous ZDV during intranatal period and oral ZDV alone or in combination with other ART medications to the newborn should be given for 6 weeks. Although intrapartum/ neonatal ARV medications will not prevent perinatal transmission that occurs before labour, most transmission occurs near to or during labor and delivery.
- Single-dose nevirapine regimen administered intrapartum to the mother and within 72 hours of delivery to the baby is not recommended as it reduces perinatal transmission by only about 50%.
- A combination of zidovudine regimen and single-dose nevirapine regimen may also be used in resource-limited areas.
- However, in well-resourced settings, use of combination antiretroviral therapy for preventing perinatal transmission has become the standard of care.

Breast Feed

- Breast milk transmission contributes significantly to MTCT rates.
- The WHO recommends that where replacement feeding is "acceptable, feasible, affordable, sustainable and safe" ("AFASS" criteria), HIV-infected women should avoid breastfeeding.
- In resource-limited situations, breast feeding is still recommended.

Q. Give a brief account of immune reconstitution inflammatory syndrome (IRIS).

- With treatment of HIV, the immunity starts getting restored and the body begins to fight aggressively against coexisting infection or partially treated opportunistic infections, thereby causing atypical manifestations of opportunistic infections. The constellation of clinical symptoms, signs or investigational parameters resulting from such inflammatory response is called immune reconstitution inflammatory syndrome (IRIS) or immune restoration disease (IRD).
- Pre-existing infections in individuals with IRIS may have been previously diagnosed and treated or they may be subclinical and later unmasked by the host's regained capacity to mount an inflammatory response.
- Thus, in IRIS, there is occurrence or worsening of clinical and/or laboratory parameters despite a favourable outcome in CD4 cell count and plasma viral loads. Both infective (clinical or subclinical) and non-infective conditions can act as triggering factors for precipitating IRIS.
- A variety of fungal, parasitic, mycobacterial and viral opportunistic infections are associated with manifestations of IRIS.
- The risk factors for IRIS include: CD4 count <50 cells/μL, a high viral load, a rapid decline in viral load, active or subclinical infection by opportunistic pathogens, initiation of HAART in close proximity to the diagnosis and initiation of treatment for an opportunistic infection.

- Non-infectious IRIS may present with cutaneous involvement (papular urticaria, eosinophilic folliculitis, Reiter's syndrome, sarcoidosis and systemic lupus erythematosus) or without cutaneous involvement (autoimmune thyroiditis, Guillain–Barre syndrome, myopathy, radiculopathy, acute porphyria, Non-Hodgkin's lymphomas and Castleman's disease).
- The infectious syndromes occur with various opportunistic infections with tuberculosis being the most common. IRIS in tuberculosis typically occurs 1–6 weeks after the patient begins ART. The signs and symptoms of tuberculous IRIS may include high fever, new or worsening lymphadenopathy (mediastinal or peripheral), worsening of pulmonary symptoms and infiltrates, or new or increasing pleural effusion. Lymph node abscesses usually occur during the first weeks on HAART.
- Differential diagnoses include failure of ART, toxicity of ART, active opportunistic infection and failure of antimicrobial therapy.
- Treatment includes continuation of primary therapy against the offending pathogen in order to decrease the antigenic load, continuation of effective HAART and judicious use of anti-inflammatory agents. In severe cases, a short course of steroids may be indicated.

Q. Discuss transmission of HIV to health-care workers.

- Major hazard to a healthcare worker (HCW) is from various body fluids of a patient. These fluids include blood and fluids from eyes, nose and mouth. Intact skin and mucous membranes of a HCW are important defences against HIV.
- Following percutaneous exposure to a needle contaminated with HIV-infected blood, the risk of transmission of HIV to a HCW is 0.13–0.5%, which is 45–120 times less than the risk of hepatitis B virus infection following similar exposure.
- Splashes of infectious material to mucous membranes or broken skin may also transmit HIV infection (estimated risk per exposure, 0.09%).
- The major risk of transmission of HIV infection to a HCW is from a patient with unknown HIV status particularly when the "universal precautions" are ignored.

Universal Precautions

- Gloves should be worn whenever there is likelihood of contact with body fluids.
- During procedures (in which there may be splashing of blood), eyes, nose and mouth should be protected with mask and protective glasses. Further, rest of the body should be protected by suitable gowns.

Q. What are the recommendations on post-exposure care of a healthcare worker?

Management of the Wound

- Wound and skin should be washed with soap and water.
- The area exposed should be soaked in povidone–iodine 10% or alcohol.
- "Squeezing out" needlestick injuries or wounds is to be avoided as it may promote hyperaemia and inflammation at the wound site, potentially increasing systemic exposure to HIV if present in the contaminating fluid.
- In case of exposure to a mucous membrane, it should be flushed with water. Topically applied povidone–iodine 10% is well tolerated by the ocular and oral mucous membranes and can be used in cases of suspected mucous membrane inoculation. However, topical alcohol on mucous membranes should be avoided.

Determine Risk Associated with Exposure

- Exposures that may warrant post-exposure prophylaxis include:
  - Parenteral or mucous membrane exposure (sexual exposure and splashes to the eye, nose or oral cavity) from following bodily fluids: blood, visibly blood stained fluid, blood stained saliva, breast milk, genital secretions and cerebrospinal, amniotic, rectal, peritoneal, synovial, pericardial or pleural fluids.
- Exposures that do not require post-exposure prophylaxis include:
  - When the exposed individual is already HIV positive;
  - When the source is established to be HIV negative;
  - Exposure to bodily fluids that do not pose a significant risk: tears, non-blood-stained saliva, urine and sweat
  - Exposure of intact skin to infectious fluids
- A known source-patient should be tested for anti-HIV, HBsAg and anti-HCV.

Post-exposure Prophylaxis (PEP) Regimens

- A regimen for post-exposure prophylaxis for HIV with two ARV drugs is effective, but three drugs are preferred.
- Tenofovir (300 mg OD) plus lamivudine (300 mg OD) (or emtricitabine 200 mg OD) are the two preferred drugs as backbone for prophylaxis.

- Lopinavir/ritonavir boosted (400 mg/100 mg BID) or atazanavir/ritonavir boosted (300 mg/100mg OD) is the preferred third agent.
- If available, raltegravir (400 mg BID) should be preferred over ritonavir-boosted PIs.
- Agents not recommended for PEP include nevirapine, delavirdine, abacavir and zalcitabine.

Time to Start HIV PEP

- PEP should be initiated promptly, preferably within 1–2 hours of post-exposure.

Duration of Prophylactic Treatment

- PEP is continued for 4 weeks.

Monitoring the Exposed Healthcare Worker

- HCW should be monitored for any serious side effects of the antiretroviral drugs.
- Complete blood counts and renal and hepatic function tests should be done at baseline and then 2 weeks after initiating chemoprophylaxis.
- Baseline HIV-antibody test and tests for hepatitis B and C infections should be done that are repeated at 4 weeks and 12 weeks post-exposure.

Chapter 4
Diseases of the Skin

Q. What are the various types of eczema? Briefly outline their clinical features and general management.

Q. Give a brief account of dermatitis.

- The terms eczema and dermatitis are used synonymously. Eczema is not a specific disease entity but a characteristic inflammatory response of the skin to both exogenous and endogenous agents.

Types

Exogenous

- Irritant contact eczema is due to detergents, alkalis, acids, solvents and abrasive dust. Strong irritants often cause acute eczema, whereas weak irritants often cause chronic eczema.
- Allergic contact eczema is due to delayed hypersensitivity reaction following contact with antigens or haptens. Previous exposure to the allergen is required for sensitization. The eczema occurs wherever the allergen contacts the skin. During the acute phase, lesions are marked by oedema, erythema and vesicle formation. As the vesicles rupture, oozing ensues and papules and plaques appear. In the chronic stage, scaling, lichenification and excoriations predominate. Face, neck and hands are the most common body parts involved. Forehead and ears are commonly affected by hair dyes and shampoos; ears are susceptible to metals from earrings; eyelids are particularly affected by airborne allergens and nail polish; the cheeks and lips are prone to react to facial cosmetics.

Endogenous

- Atopic eczema (or atopic dermatitis) is due to a genetic predisposition to form excessive IgE antibodies to inhaled, injected or ingested antigens.
  - Patients with atopic eczema have a tendency to develop other allergic diseases like asthma, allergic rhinitis, hay fever, urticaria, food and other allergies. Many have family history of allergic disorders.
  - More than 95% cases develop before the age of 5 years.
  - The cardinal features of atopic eczema are itch, erythema, xerosis, oedema, oozing, crusting and lichenification. Pruritus is the hallmark of it.
  - Primarily flexural (antecubital and popliteal fossae) in its distribution in children and adults, but facial and truncal involvement predominates in infants.
  - Usually chronic or relapsing.
  - By adulthood, 40% to 80% of patients will experience either a decrease or complete resolution of their disease.
- Seborrhoeic eczema often runs in families and is associated with a tendency to dandruff.
  - Possibly due to excessive growth of fungi of the genus *Malassezia* (formerly called *Pityrosporum*).
  - Not a disorder of sebaceous glands.
  - High prevalence in HIV-infected persons particularly if CD4 cell count is <400/mm^3.
  - Patient has characteristic "seborrhoeic look"—oily skin with patulous, prominent follicular orifices.
  - Involves areas rich in sebaceous glands—scalp, retroauricular folds, eyebrows, nasolabial folds, beard area, interscapular and pre-sternal regions, axillae, pubic region, groin, umbilicus and folds under pendulous breasts.
  - Scalp area—diffusely involved with greasy scales on a dull red background.
  - Intertriginous areas—erythematous scaly lesions or exudative crusted lesions.
  - Eyebrows—fine scaling of eyelid margins.
  - An infantile form, which usually involves the scalp (cradle cap), the face and the diaper area, affects as many as 70% of newborns during the first 3 months of life but usually disappears by 1 year of age.
- Discoid eczema (nummular eczema) is seen most often on the limbs of elderly males, and is of uncertain aetiology. Coin-sized eczematous patches are seen.

- Asteatotic eczema is commonly seen on the lower legs in hospitalised elderly patients.
- Gravitational (stasis) eczema occurs on the lower legs and is often associated with signs of venous insufficiency.
- Pompholyx (dyshidrotic eczema) describes a form of eczema in which bouts of recurrent vesicles or bullae affect the palms, fingers and soles.

General Management

General

- Emollients and moisturizers are helpful for moisturizing the skin. Ointments are preferred over creams because creams may contain potentially sentisizing preservatives and mildly irritating emulsifiers.

Atopic Eczema

- Explanation, reassurance and encouragement.
- Avoidance of heat, dryness and contact with irritants.
- Oral antihistamines.
- Topical steroids should be used judiciously. The various preparations available are 1% hydrocortisone (mildly potent), clobetasone butyrate (moderately potent), betamethasone valerate (potent) and 0.05% clobetasol propionate (very potent) and their use depends on severity of lesions.
- Topical calcineurin inhibitors (tacrolimus and pimecrolimus) are a new class of topical immunomodulators and are useful if steroids are not effective. However, these agents cannot be used for erosions and ulcers.

Seborrhoeic Eczema

- Ordinary shampooing in mild cases with scalp involvement.
- In severe cases, medicated shampoos containing selenium sulphide (2.5%), zinc pyrithione (1%) or ketoconazole (2%). For facial lesions, topical ketoconazole cream (2%) or topical calcineurin inhibitors may be used.
- Topical lithium succinate and lithium gluconate are effective alternative agents for the treatment of seborrhoeic eczema in areas other than the scalp.
- In acute stage, topical steroids of low potency to control erythema and itching.

Q. Discuss aetiology and management of xerostomia.

- Daily production of saliva in healthy adults is approximately 1500 mL.
- Xerostomia—a subjective complaint of dry mouth, which may result from a decrease in the production of saliva.
- Effects of xerostomia:
    - Symptoms may be minor for some, while for others they may hamper activities of daily living.
    - May cause burning sensation in mouth, difficulty in eating, chewing and swallowing.
    - May cause serious health problems, such as tooth decay, bad breath, candida infection and viral infections (e.g. herpes simplex).

Aetiology

- Anticholinergic drugs (reduce volume of saliva)	Anticholinergics, antidepressants, antiemetics, antihistamines, antihypertensives, antiparkinsonian drugs, antipsychotics, antispasmodics, diuretics
- Sympathomimetic drugs (produce viscous saliva)	Amphetamines, appetite suppressants, bronchodilators, decongestants
- Systemic causes	Addison's disease, Alzheimer's diseases, alcoholic cirrhosis, diabetes mellitus, HIV/AIDS, radiation to head and neck area (e.g. for cancer therapy), salivary gland infection, severe dehydration, Sjogren's syndrome
- Others	Elderly persons, sleep-related xerostomia (due to mouth-breathing during sleep)

Management

- Stop the offending drug if possible.
- Oral hygiene including chlorhexidine rinses.
- Frequent sips of water and teeth brushing.

- Artificial salivary substitutes—intended to act as a replacement of lubricative and protective function of the natural saliva and not as substitutes for digestive and enzymatic actions. Examples include sodium carboxymethylcellulose, potassium dihydrogen orthophosphate and sorbitol.
- Cholinergic agonists:
  - Pilocarpine and cevimeline.
  - Cautious use in patients with cardiovascular disease and chronic respiratory conditions.
  - Contraindicated in patients with uncontrolled asthma, angle-closure (narrow angle) glaucoma and liver disease.

Q. Discuss briefly about pruritus.

- Defined as a cutaneous sensation that provokes the desire to scratch. It is intended to serve a protective function to remove pruritogenic stimuli.

Pathophysiology

- Pruritus originates in the terminal nerve endings within the skin and can be elicited by inflammation, dryness, contact exposure and other allergic responses.
- In allergic responses, histamine is the mediator in many cases.
- In some conditions such as chronic kidney disease, cholestasis and lymphoma, serotonin may play a role. It excites nociceptive C-fibres, which in turn produce itching.

Aetiology

- Can be due to a dermatological or systemic cause.
- Localised itching is rarely caused by a systemic process.
- Pruritus may precede the development of a systemic disease by several years.

Dermatological causes	Systemic causes
- Xerosis - Atopic dermatitis - Contact dermatitis - Folliculitis - Psoriasis - Scabies - Drug eruption (e.g. angiotensin-converting enzyme inhibitors, salicylates, chloroquine, and calcium channel blockers)	- Hepatic diseases: - Cholestasis - Hepatitis - Renal disease: - Chronic renal failure - Haematologic diseases: - Polycythaemia vera - Iron deficiency anaemia - Endocrine diseases: - Thyroid diseases - Carcinoid syndrome - Malignant diseases: - Solid tumours - Lymphomas - Leukaemias - Others: - AIDS

Complications of Pruritus

- Lichen simplex chronicus (localised skin thickening due to intense scratching).
- Prurigo nodularis (variant of lichen simplex chronicus where nodules develop at the site of itching).
- Local infection.

Treatment

General Measures

- Controlling xerosis with moisturisers and humidification of indoor environment.
- Use of antihistamines like diphenhydramine.

Specific Measures
- Treatment of underlying cause.
- Ursodexoycholic acid (UDCA) in cholestasis.
- Cholestyramine, rifampicin and opioid antagonists (e.g. naltrexone) in primary biliary cirrhosis.
- Ultraviolet B phototherapy, gabapentin and ondansetron in uraemic patients.
- Corticosteroids in patients with Hodgkin's disease.
- Paroxetine, a selective serotonin reuptake inhibitor, is useful in itching produced as paraneoplastic manifestation of malignancies. It may also be used in other causes of pruritus.
- Indomethacin for HIV-associated itching.

Q. Briefly outline the clinical manifestations and management of psoriasis.

- The main abnormality in psoriasis is the increased epidermal proliferation due to excessive division of cells in the stratum basale and a shorter cell cycle. In association with the basal cell hyperplasia, there is enhanced metabolism and accelerated synthesis and degradation of nucleoproteins, resulting in hyperuricaemia. There is proliferation of the subepidermal vasculature, which is responsible for the "Auspitz's sign". T lymphocytes are important in the pathogenesis.
- Commonly presents before the age of 35 years. It is equally common in both males and females.
- May be a presenting sign of HIV infection.
- The characteristic lesions are pink-red, sharply demarcated papules and rounded plaques, and are covered by silvery scales (plaque psoriasis).
- The most common areas of involvement are the extensor body areas (elbows and knees), gluteal cleft and the scalp. Trunk is also commonly involved. Traumatised areas are often involved (Koebner or isomorphic phenomenon) and this explains common involvement of elbows and knees.
- Besides typical lesions described above, the skin lesions can range from small drop-shaped papules (guttate psoriasis,— frequently affect children and adolescents following a streptococcal infection or an upper respiratory tract infection) to pustules (pustular psoriasis,—multiple tender sterile pustules with an underlying, blotchy, and erythematous base), to generalised erythema and scales (erythrodermic psoriasis,—develops if existing psoriasis is poorly controlled, systemic medication are withdrawn suddenly, reaction to a drug such as lithium, or presence of an underlying systemic infection). Another type of psoriasis is inverse psoriasis characterized by lesions in the skin folds.
- About half of the patients have finger nail involvement. The characteristic nail changes are punctate pitting, onycholysis (separation of nail from the nail bed) and subungual hyperkeratosis.
- On scrapping a psoriatic lesion with a microscopic slide, silvery scales come out first. After that, pin-point bleeding appears at the base of the lesion. The latter is known as Auspitz's sign.
- Psoriatic arthritis is seen in 5–10% of psoriatic patients and usually occurs several years after appearance of skin lesions. It is a form of seronegative spondyloarthropathy.
- Medical co-morbidities: Some of the co-morbidities associated with psoriasis include ulcerative colitis, Crohn's disease, coronary artery disease, metabolic syndrome and lymphoma.

Treatment

- Most patients with psoriasis have skin lesions limited to localised areas. For these patients, topical therapy remains a part of their therapeutic regimen.

Local Treatment

- Local measures include application of emollients, coal tar preparations, dithranol, topical steroids, and ultraviolet radiation (narrowband UVB and PUVA). Topical steroids range in strength from weak steroids such as 1% hydrocortisone to superpotent corticosteroids, such as clobetasol propionate and betamethasone dipropionate. Side effects of topical corticosteroids, especially those that carry the superpotent categorisation include cutaneous atrophy, development of striae and formation of telangiectasia. Hypothalamic–pituitary–adrenal axis suppression can occur with prolonged use.
- Other local agents include vitamin D analogues that inhibit keratinocyte growth, promote keratinocyte differentiation, and decrease inflammation in psoriatic lesions via vitamin D receptors on keratinocytes and T lymphocytes. These include calcipotriol, calcitriol and tacalcitol.
- Local retinoid, tazarotene, is also useful.
- Calcineurin inhibitors (tacrolimus and pimecrolimus) improve symptoms with less skin atrophy than topical corticosteroids and are considered first-line treatments for facial and flexural psoriasis.

Systemic Treatment

- Systemic treatment is necessary in extensive psoriasis that fails to respond to the local measures. The most commonly used treatments are photochemotherapy with PUVA (psoralens with ultraviolet A), retinoids (etretinate and acitretin), methotrexate and cyclosporin.
- In PUVA therapy, after ingestion or local application of a psoralen preparation, patients are then exposed to UVA that activates the psoralens. Once activated, psoralens cross-link DNA strands preventing replication of keratinocytes and induce death of activated T cells in skin. In India, an alternative to UVA light is to ask the patient to sit in the sunlight. However, long-term PUVA treatment may lead to an increased risk of squamous cell carcinoma and possibly malignant melanoma.
- Methotrexate is one of the most effective treatments for psoriasis and psoriatic arthritis. However, it has a number of side effects including bone marrow toxicity, nausea, aphthous stomatitis and development of megaloblastic anaemia. Chronic administration of methotrexate has been associated with the development of hepatic fibrosis.
- Etretinate has a long half-life; therefore, it should not be prescribed to females of childbearing potential due to the risk of long-term teratogenicity. Acitretin, the active metabolite of etretinate, has a shorter half-life and therefore, can be given to females as long as they are not planning a pregnancy for 3 years after discontinuing its use.
- Cyclosporin (2.5–5 mg/kg for 10–12 weeks) is highly effective oral therapy for psoriasis. The side effects include hypertension, nephrotoxicity, hypomagnesaemia, hyperkalaemia, hyperuricaemia, elevation of liver transaminases, development of paraesthesias and hypertrichosis.

Biological Therapy

- Includes drugs produced by living organisms to target specific points of inflammation cascade, including antibodies against cell surface markers, cytokines and adhesion molecules.
- Indicated in patients with severe disease not responding to other measures.
- Includes alefacept (causes apoptosis of T cells), efalizumab (inhibits T cell activation), etanercept, infliximab and adalimumab (TNF-inhibitors).

Q. Discuss the aetiology, clinical features, diagnosis and treatment of erythema nodosum.

- Erythema nodosum is inflammation of subcutaneous fat (panniculitis) of skin.
- It develops as a result of a non-specific cutaneous reaction to a variety of antigens, with many immune-mediated mechanisms implicated including immune-complex mediated reaction and type IV delayed hypersensitivity response to antigens.

Aetiology

Common causes
- Idiopathic (most common)
- Infections: Streptococcal pharyngitis, mycobacterial (tuberculosis—usually primary, leprosy), mycoplasma, chlamydia, yersinia, histoplasmosis
- Sarcoidosis
- Drugs: Antibiotics (e.g. sulphonamides, amoxycillin), oral contraceptives
- Pregnancy
- Inflammatory bowel disease: Ulcerative colitis, Crohn's disease

Rare causes
- Viral infections: Herpes simplex virus, Epstein–Barr virus, hepatitis B and C viruses, human immunodeficiency virus
- Bacterial infections: Syphilis, *Campylobacter* spp., rickettsiae
- Parasitic infections: Amoebiasis, giardiasis
- Miscellaneous: Lymphoma, other malignancies

Clinical Features

- More common in females (male-to-female ratio, 1:6).
- Can occur at any age with peak incidence between 20 and 30 years.
- A prodrome commonly occurs before the onset of erythema nodosum regardless of aetiology. Features of prodrome include weight loss, malaise, low-grade fever, cough and arthralgia with or without arthritis. Arthralgias may persist for several months after resolution of erythema nodosum.

- Presents with painful, symmetrical, erythematous nodules and plaques ranging in size from 1 to 10 cm. Nodules are poorly demarcated due to their subcutaneous location and are most commonly located on the anterior aspect of legs, particularly shins, ankles and knees. Within a few days, the nodules become livid red or purplish colour. Finally, they exhibit a yellow or greenish appearance often taking on the look of a deep bruise (erythema contusiformis). This contusiform colour evolution is quite characteristic of erythema nodosum and allows a specific diagnosis in late-stage lesions. Ulceration is never seen and the nodules heal over several weeks without atrophy or scarring.
- Less frequent clinical manifestations associated with erythema nodosum are lymphadenopathy, hepatomegaly, spleno-megaly, and pleuritis.
- In children, erythema nodosum has a much shorter duration than in adults, arthralgias are seen in a minority of the patients, and fever is less common.

Diagnosis

- Most often, diagnosis is based on clinical presentation.
- If required, a deep biopsy should be obtained for best results. It shows an inflammation of the septa in the subcutaneous fat tissue (septal panniculitis). Erythema nodosum is not associated with vasculitis, although small vessel inflammation and haemorrhage can occur.
- Diagnosis of cause of erythema nodosum:
  - Complete blood count with differential; erythrocyte sedimentation rate and C-reactive protein level.
  - Evaluation for streptococcal infection (i.e. throat culture for group A streptococci, rapid antigen test, antistreptolysin-O titre, and polymerase chain reaction assay).
  - Chest radiograph for tuberculosis and sarcoidosis.
  - Stool examination for ova and parasites in patients with gastrointestinal symptoms.
  - Consider evaluation for inflammatory bowel disease if symptoms are present.

Treatment

- Treat any underlying disorders.
- Rest and analgesics with NSAIDs. However, NSAIDs should be avoided in treating erythema nodosum secondary to Crohn's disease because they may trigger a flare-up of the underlying Crohn's disease.
- Potassium iodide is given orally (400 to 900 mg/day) for symptomatic relief if NSAIDs do not relieve pain or the lesions persist. It is contraindicated during pregnancy.
- Systemic steroids may be given if underlying infection and malignancy have been excluded.

Q. Briefly outline the aetiology, clinical features and management of acne vulgaris.

- This is a disorder characterized by chronic inflammation of blocked pilosebaceous follicles. It predominantly affects teenagers.

Aetiopathogenesis

- There is an increase in sebum excretion, which is probably androgen mediated.
- Increased and abnormal keratinisation at the exit of the pilosebaceous follicle causes obstruction to the flow of sebum.
- The sebum of patients with acne contains an excess of free fatty acids that may be responsible for triggering the inflammatory process.
- Colonisation by pathogenic *Propionibacterium acnes* causing inflammation at a later stage of the disease.
- Important endocrine causes of acne include polycystic ovarian syndrome, Cushing's syndrome, congenital adrenal hyperplasia, androgen-secreting tumours of adrenals, ovary and testis, and acromegaly.

Pathophysiology

- Abnormal keratinocyte proliferation and desquamation which leads to obstruction of ducts of sebum glands
- Androgen driven increase in sebum production
- Proliferation of *Propionibacterium acnes*
- Inflammation.

- A number of drugs can produce acne. The lesions are usually on the trunk rather than on face. Some of the commonly used drugs are listed in the box.

• **Glucocorticoids:**	Systemic and local agents
• **Anabolic:**	Danazole, stanazole
• **Antiepileptics:**	Phenytoin, carbamazepine, topiramate, gabapentin
• **Antidepressants:**	Amitryptyline, lithium, sertraline
• **Antitubercular:**	Isoniazid, rifampicin
• **Chemotherapeutic agents:**	Dactinomycin, pentostatin, gefitinib
• **Antiviral:**	Ritonavir, ganciclovir
• **Vitamins:**	B_6, B_{12}

Clinical Features

- Lesions are limited to the face, shoulders, upper chest and back.
- Seborrhoea (greasy skin) is often present.
- Open comedones (blackheads) are due to plugging of the pilosebaceous orifice by keratin and sebum.
- Closed comedones (whiteheads) are due to accretions of sebum and keratin deeper in the pilosebaceous ducts.
- Later in the course, inflammatory lesions occur that tend to lead to more scarring. The lesions may include papules, pustules, nodules and cysts, and any combination of these. Severe forms of inflammatory acne include nodular cystic disease with all its potentially destructive sequelae.

Management

- General measures:
  - Regular washing with soap and water.
  - Antibacterial skin cleansers containing chlorhexidine.
- Local measures:
  - Keratolytics include α- and β-hydroxy acids, azelaic acid and retinoids. Tretinoin is the most potent keratolytic agent. Other retinoids include isotretinoin (less effective), adapalene (less irritating) and tazarotene. Topical retinoids may produce skin irritation, sun sensitivity and initial flaring of acne.
  - Reducing infection by *P. acnes* by using benzyl peroxide and local antibiotics. Benzoyl peroxide commonly causes dry skin and occasionally allergy. It has mild but significant keratolytic effect. It inactivates topical retinoic acid when used concurrently and may cause skin bleaching. Topical antibiotics include clindamycin and erythromycin.
  - Usually, topical benzoyl peroxide or antibiotic is applied in the morning and a keratolytic preparation at night.
- Systemic measures:
  - Long-term antibiotic therapy with doxycycline, minocycline or erythromycin for duration of 3 months to 2 years. Erythromycin is less effective due to development of resistance in *P. acnes* but is used if tetracyclines cannot be used.
  - Isotretinoin (13-*cis*-retinoic acid) given orally in a 4-month course can reduce sebum excretion and may be required in severe acne. Oral isotretinoin is a potent teratogen and may be associated with development of mood disorders, depression, suicidal ideation, hepatotoxicity and hypertriglyceridaemia. It is contraindicated during pregnancy due to its teratogenic effects.
  - Hormonal treatment:
    - Androgen receptor blockers:
      - Spironolactone, cyproterone acetate, drospirenone and flutamide.
      - Cyproterone acetate is combined with oestrogen and is given in courses as an oral contraceptive.
    - Inhibitors of adrenal androgen production:
      - Low-dose glucocorticoids in acute and severe acne.
    - Inhibitors of ovarian androgen production:
      - Oral contraceptives containing oestrogen in the form of ethinyl oestradiol combined with a progestin.
- Physical measures:
  - Incision and drainage of cysts.
  - Intralesional injections of triamcinolone acetonide.
  - Light (blue light with wavelength of 407–420 nm) and laser treatment.
  - Photodynamic therapy using aminolevulinic acid or indocyane green dye application.

Q. Briefly outline the precipitating causes, clinical manifestations and management of erythema multiforme.

Q. Give a brief account of target lesions, iris lesions and bull's eye lesions.

Q. Write a short note on Stevens–Johnson syndrome.

Q. Briefly outline toxic epidermal necrolysis.

- Erythema multiforme (EM) is an acute, self-limiting and sometimes recurring skin condition considered to be a hypersensitivity reaction associated with certain infections and medications.
- Previously, EM was thought to be part of a clinical spectrum of disease that included erythema minor, erythema major (often equated with Stevens–Johnson syndrome—SJS) and toxic epidermal necrolysis (TEN).
- Although SJS and TEN may represent the same process with differing severity, EM with its minimal mucous membrane involvement and less than 10% epidermal detachment is now accepted as a distinct condition.

Causes

- EM can be induced by a variety of viral (including dengue and CMV), bacterial and mycoplasma infections. In addition, a number of drugs have been implicated, the most common being sulphonamides, phenytoin, barbiturates, penicillins, carbamazepine, abacavir, allopurinol, macrolides, tetracyclines and nevirapine. Herpes simplex virus infection is the most common recognizable cause of EM.
- The most common cause of SJS and TEN are medications. These are T cell-mediated diseases with CD8+ cells acting as the major mediator of keratinocyte death.
- HLA-B*1502 and HLA-B*5701 respectively implicated in carbamazepine and abacavir-induced SJS/TEN.

Clinical Features

Erythema Multiforme

- Usually occurs in adults 20–40 years of age.
- A self-limited eruption with usually mild or no prodromal symptoms.
- Patients may experience itching and burning at the site of the eruption.
- Individual lesions begin acutely as numerous sharply demarcated red or pink macules that then become papular. The papules may enlarge gradually into plaques several centimetres in diameter. The central portion of the papules or plaques gradually becomes darker red, brown, dusky or purpuric. Crusting or blistering sometimes occurs in the centre of the lesions.
- The characteristic "target" or "iris" lesion has a regular round shape and three concentric zones: a central dusky or darker red area, a paler pink or oedematous zone and a peripheral red ring.
- Common sites of involvement are hands, extensor part of forearms, palms, soles and mucous membranes of mouth, nose, eyes and genitalia.
- Mucosal lesions may occur in about 30-50% cases but are mild and usually limited to the oral cavity. Lesions vary from diffuse oral erythema to multifocal superficial ulcerations. Initially, vesicles or bullae may also be present.
- The lesions resolve spontaneously in 3–5 weeks without sequelae, but may recur.

Stevens–Johnson Syndrome

- Characterized by skin and ≥2 mucous membranes involvement.
- Skin involvement is characterized by confluent purpuric macules, sometimes blisters, on the face and trunk. Target lesions are not seen and the epidermal detachment does not involve >10% of the surface area. Nikolsky sign is often positive.
- Involvement of oral and/or mucous membranes may be severe enough that patients may not be able to eat or drink.
- Usually, it is accompanied by severe constitutional symptoms in the form of fever, tachycardia and hypotension. Electrolyte imbalance is frequent.
- Patients with genitourinary involvement may complain of dysuria or an inability to void.
- Severe ophthalmic involvement may lead to permanent scarring and blindness.
- Epithelial loss results in vulnerability to bacterial infections and predisposes to septicaemia.
- Mortality approximately 5%.

SJS/TEN Overlap

- Skin involvement is between 10-30%.
- Systemic features are present.

Toxic Epidermal Necrolysis (Lyell Syndrome)

- Begins with severe mucosal erosions and progresses to diffuse, generalised detachment of the epidermis. Nikolsky sign is often positive.
- Target lesions are not seen.
- More than 30% skin is involved.
- Mortality as high as 30%.

Management

- Management of the primary causes (discontinuation of medications and treatment of infection).
- Mild cases do not require any specific treatment. Antihistamines and local corticosteroids may provide symptomatic relief.
- Severe cases may require systemic corticosteroids.
- Oral acyclovir early in herpes-associated outbreaks of EM is useful to lessen the number and duration of lesions.
- Continuous acyclovir is helpful if recurrent herpes-associated EM develops.
- In SJS and TEN, fluid and electrolyte balance must be maintained. Manage oral lesions with mouthwashes. Topical anaesthetics are useful in reducing pain and allowing the patient to take fluids. Areas of denuded skin must be covered with compresses of saline. Role of systemic steroids and intravenous immunoglobulins is controversial.

Q. Describe the aetiology, clinical features and management of staphylococcal toxic shock syndrome.

- A toxin-mediated disease characterized by rapid onset of generalised erythema with desquamation, fever, hypotension and potential multisystem failure.

Aetiology

- Occurs due to exotoxin produced by *Staphylococcus aureus*.
- Common in women using menstrual tampons of high absorbency and in patients with superficial skin or surgical wound infections.
- *S. aureus* elaborates exfoliative toxins which induce massive cytokine secretion by T-cells, leading to fever, hypotension and multiorgan failure.

Clinical Features

- After a 2–3 day prodrome period of malaise, patients typically present with fever, chills, nausea and abdominal pain.
- A diffuse erythematous, non-pruritic, maculopapular or petechial rash ensues that subsequently desquamates.
- Rash initially appears on the trunk and spreads peripherally to involve palms and soles.
- Multisystem involvement includes cardiac arrhythmias, hepatic and renal failure, disseminated intravascular coagulation, and acute respiratory distress syndrome. Mucous membranes are spared.

Management

- Removal of inciting factors, including removal of tampon.
- Aggressive treatment of hypotension and of potential multiorgan failure.
- Antistaphylococcal antibiotic therapy.

Q. Briefly outline keloid and hypertrophic scar.

- More commonly observed in Asians and dark skinned races; this association is less commonly seen with hypertrophic scars.
- May follow local skin trauma or inflammatory skin disorders like laceration, tattoos, burns, injections, ear-piercing, vaccination, bites, acne, abscess or surgery.
- Occur due to uncontrolled synthesis and deposition of dermal collagen.
- Wounds subjected to tension due to motion, body location or loss of tissue are at increased risk of scar hypertrophy and keloid formation.
- Hypertrophic scar usually appears within a month of injury, whereas keloids may take three months or even years to develop.

Clinical Features

- A keloid extends beyond the borders of the original wound, does not regress spontaneously, grows in pseudotumour fashion with distortion of the lesion and tends to recur after excision. Itching and pain are common. It has a firm and inflexible texture, a shiny appearance, and are usually flesh-coloured, but may be erythematous or hyperpigmented.
- Hypertrophic scars remain confined to the borders of the original wound and most of the times retain their shape. Itching may occur.

Differences between Keloid and Hypertrophic Scar

Keloid	Hypertrophic scar
• Associated with dark skin colour	• Not associated with dark skin colour
• Generally develops months after injury	• Develops within a month of injury
• Does not regress with time	• Generally regresses with time
• Extends beyond borders of original wound	• Remains confined to borders of wound
• Commonly occurs on sternal skin, shoulders, upper arms, earlobes and cheeks	• Arises in any location but usually on extensor surfaces of joints
• Worsened by surgery	• Improves with surgery

Treatment

- Treatment modalities include compression garments, radiation, excision, intralesional injections, cauterisation, cryotherapy, laser surgery and silicone gel dressings.
- Excision of keloid with scalpel, electrosurgery or laser surgery will result in almost 100% chances of recurrence. Keloids over areas like ear lobes are less likely to recur.
- Surgical excision of hypertrophic scars may be efficacious in selected cases but requires meticulous adherence to the surgical principles and adjunctive measures like radiation, intralesional interferon or topical imiquimod.
- Intralesional injections are useful in the treatment. Various agents used for injection include triamcinolone, 5-fluorouracil, bleomycin and interferon-α-2b.
- Freezing the lesions of keloid with liquid nitrogen (cryotherapy) helps to soften the lesions, which makes the intralesional administration of medication easier.

Q. Write briefly about the aetiology, clinical features and treatment of vitiligo.

- Occurs due to selective destruction of the skin melanocytes that results in development of unsightly depigmented patches.
- Onset before the age of 18 years in more than 50% cases.
- Vitiligo can be separated into segmental and non-segmental (vitiligo vulgaris). Segmental vitiligo has important differences in etiology, prevalence of associated illnesses and therapy compared to other forms of vitiligo.

Aetiology

- Non-segmental vitiligo is most commonly described as having an autoimmune etiology. Both humoral and T cell mechanisms are possibly involved in pathogenesis.
- Segmental vitiligo is possibly due to some chemical mediators released from peripheral nerve endings that cause decreased production of melanin (neural theory).

Clinical Features

- Presents as small, depigmented lesions which may enlarge and coalesce into larger patches.
- Vitiligo is most striking around the body orifices: eyes, nostrils, mouth, nipples, umbilicus and genitalia.
- Vitiligo can affect melanocytes in the hair roots resulting in patches of white hair. Depigmentation can affect mucosal areas such as in the mouth or genitalia.
- In non-segmental vitiligo, lesions are usually symmetrical and new patches may appear throughout the patient's life. It may be either generalised or localised. The overlying hair may remain pigmented or turn white. This type of vitiligo is often associated with a number of immune system aberrations. Childhood, non-segmental vitiligo is frequently associated with autoimmune thyroiditis. To the contrary, vitiligo in adults is quite strongly associated with a number of autoimmune disorders, including alopecia areata, diabetes mellitus, pernicious anaemia, Addison's disease and Hashimoto's thyroiditis.
- Segmental vitiligo usually has unilateral involvement and a dermatomal distribution. Without treatment, lesions are typically persistent throughout developing within 2 years of onset. It is typically associated with leukotrichia (white hair). It has no association with autoimmune thyroiditis and is in fact rarely associated with any autoimmune disease.
- Koebner phenomenon: Non-segmental vitiligo can spread by Koebner phenomenon. Other skin conditions that can also spread by Koebner phenomenon include psoriasis and lichen planus. The Koebner phenomenon is the initiation of new lesions that occur as a result of trauma, particularly mechanical trauma such as scratching.

- Use of a Woods light with UV light in the range of 320–400 nm can greatly assist in locating areas of pigment disruption. A complete examination should include inspection of the genitalia and areas of skin folds as these areas can be easily overlooked.

Treatment

- Topical psoralen plus ultraviolet A (UVA) phototherapy (PUVA therapy) is a well-established treatment for non-segmental vitiligo (less effective in segmental vitiligo). Topical application of psoralen is followed half an hour later by exposure to long UV rays (320–400 nm) from sunlight or artificial light sources. However, it is effective in only about half of the patients and has a high relapse rate. Common side effects include darkening of normal skin, erythema, scaling, and pruritus. Less common side-effects include phototoxic effects, photoallergic reactions, hyper-keratosis of lesional skin, and rarely, skin malignancies. Another less toxic agent is khellin which is used with UVA.
- Narrow-band UVB (NB-UVB) phototherapy is the treatment of choice for patients with active, spreading lesions or those with generalised (>20% of body surface area) vitiligo. Cosmetic results are better and side effects are less with this therapy compared to PUVA.
- Local application of corticosteroids with or without UVA exposure is effective in many patients.
- Targeted phototherapy using the excimer laser is useful in treating localised vitiligo. The targeted exposure of this strategy spares the normal skin from potentially harmful radiation.
- Local application of calcineurin-inhibitors (pimecrolimus and tacrolimus) is also effective.
- Surgical modalities are quite effective in treating certain types of vitiligo. Autologous skin grafting is a method of choice for treating stable and focal vitiligo.
- Extensive vitiligo may be treated with removal of pigment from the remaining normally pigmented skin. Bleaching creams used for this purpose include monobenzyl ether of hydroquinone and 4-methoxy-phenol. Another option is to give oral psoralen after a meal followed 2–3 hours later by exposure to long UV rays.

Q. Name a few conditions which can cause hyperpigmentation.

• Ephelides (freckles)	• Lichen planus pigmentosus
• Melasma (chloasma)	• Discoid lupus erythematosus
• Acanthosis nigricans	• Drug-induced melanosis (e.g. clofazimine, minocycline, antimalarial-induced)
• Fixed drug eruptions	• Agyria
• Café-au-lait spots	• Ochronosis

Q. What are café au lait Explain.

- Well-circumscribed, evenly pigmented macules ranging in size from 1 to 2 mm to greater than 20 cm.
- Histologically, increased melanin content of both melanocytes and basal keratinocytes are seen.
- Morphologically, these spots may be either oval and smooth bordered, resembling the "coast of California," or with jagged contours resembling the "coast of Maine."
- Café au lait with smooth borders is more typical of the café au lait spots seen in neurofibromatosis type 1 (NF-1) whereas those with jagged borders are more indicative of the café au lait spots seen in McCune–Albright syndrome although variations are common.
- Solitary café au lait spots are common birthmarks. Although most café au lait spots are present at birth, they may also manifest within the first few years of life. In general, it is unusual for additional sporadic café au lait to develop after the age of 6 years; in NF-1, however, new café au lait spots may continue to develop throughout childhood and adulthood.
- In fair-skinned infants they may be difficult to perceive on routine physical examination, but may be accentuated with examination under a Wood's lamp.
- café au lait spots may develop anywhere on the body, although they more commonly occur on the torso, buttocks and lower extremities and are uncommon on the face.

McCune–Albright Syndrome

- A rare, sporadic disorder.
- Cardinal features include polyostotic fibrous dysplasia, precocious puberty and other endocrinopathies (e.g. hyperthyroidism, hyperparathyroidism, and acromegaly) and large, and irregular segmental café au lait that typically involve the torso or buttocks. Two of these features are required for diagnosis.

Q. Give a brief account of scabies.

Q. What is Norwegian or crusted scabies?

- An intensely itchy dermatosis caused by the mite *Sarcoptes scabiei* var *hominis*.
- Occurs at all ages but particularly in children.

Mode of Transmission

- Highly contagious and person-to-person spread occurs via direct contact with the skin.
- Transfer from clothes and bedding if contaminated by infested people immediately beforehand.

Pathogenesis

- Infestation occurs when the pregnant female mite burrows into the skin and lays eggs.
- After 2 or 3 days, the larvae emerge and dig new burrows. They mature, mate and repeat this cycle every 2 weeks.
- The main symptoms of scabies are probably a result of the host immune reaction to the burrowed mites and their products.

Clinical Features

- Incubation period is 3 weeks. In cases of re-infestation, symptoms develop in 1–3 days.
- Patients with scabies complain of itching, which is most severe at night.
- Other skin manifestations include papules, blisters, nodules and eczematous changes.
- These lesions commonly involve web spaces, flexor surface of wrists, axillae, waist, feet, ankles, lower portions of buttocks and genital areas.
  - In females, itching of the nipples associated with generalised pruritic papular eruption is characteristic.
  - In males, itchy papules on the scrotum and penis are virtually pathognomonic.
  - In infants and young children, scabies often affects face, head, neck, scalp, palms and soles and there is often generalised skin involvement.
- The pathognomonic sign is burrow, the linear tunnel in which the mites live. These occur as short, wavy, scaly, grey lines on the skin surface and are most easily found on hands and feet, particularly in the finger web spaces, thenar and hypothenar eminences, and on the wrists. They are often missed if the skin has been scratched, has become secondarily infected or if eczema is present.
- Secondary infection can occur with *Staphylococcus*, *Streptococcus* or both.

Crusted or Norwegian Scabies

- Crusted scabies, also known as Norwegian scabies (because of its initial description in Norwegian patients with leprosy), occurs in patients with neurological disorders or immunosuppression including HIV.
- The number of mites escalate rapidly due to impaired immune response, lack of pruritus or patient's physical inability to scratch.
- Presents with marked thickening and crusting of the skin, particularly on the hands, although the entire body including the face and scalp is often involved.
- Nails often show hyperkeratosis.
- Transmission via fomites is possible as mites survive on the sloughed skin in the environment.

Diagnosis

- Scabies is usually diagnosed on history and examination.
- Definitive diagnosis relies on microscopic identification of mites or eggs from skin scrapings of a burrow.

Treatment

- It is important to treat all members of the affected household at the same time.
- All clothes and bed linen should be washed at temperatures above 50°C. Items that cannot be laundered may be kept in a sealed plastic bag for at least 48 to 72 hours or in a freezer at –20°C for 72 hours.

Topical Treatment

Sulphur

- It is the oldest antiscabietic that is used as an ointment (2–10%).
- After a bath, sulphur ointment is applied and thoroughly rubbed into the skin over the whole body for 2–3 consecutive nights.

- Topical sulphur ointment is messy, malodorous, stains clothing, and may lead to irritant dermatitis in hot and humid climate.
- It has the advantage of being cheap. It is also a safe alternative for the treatment of scabies in infants, children and pregnant females.

Benzyl Benzoate

- Benzyl benzoate is used as a 25% emulsion and the contact period is 24 hours.
- It should be applied below the neck three times within 24 hours without an intervening bath.
- It can also cause irritant dermatitis on the face and scrotum.
- It is to be avoided in children less than 2 years of age. Although no adverse effects have been noted during pregnancy, it should be used if sulphur or permethrin are not available.

Crotamiton

- Crotamiton is used as 10% cream or lotion.
- It is applied twice daily for 5 consecutive days after bathing and changing clothes.
- The success rate varies between 50 and 70%.
- It has some antipruritic effects.

Malathion

- Malathion is an organophosphate insecticide that irreversibly blocks the enzyme acetylcholinesterase.
- It is rarely used because of the potential for severe adverse effects.

Lindane

- Lindane, also known as gamma benzene hexachloride, acts on the central nervous system of insects and leads to increased excitability, convulsions and death.
- A single 6-hour application of 1% cream is effective in treatment of scabies.
- It can rarely cause CNS toxicity, convulsions and death. To reduce its adverse effects, it should be applied on a cool, dry skin for only 6 hours after which whole body is washed with soap and water.
- It should not be used in infants, pregnant patients or if the skin is inflamed and excoriated.

Permethrin

- Permethrin is a synthetic pyrethroid and potent insecticide.
- It is very effective against mites with a low mammalian toxicity.
- Permethrin 5% dermal creams are applied overnight once a week for 2 weeks to the entire body, including the head in infants. The contact period is about 8 hours.
- It can be safely used in children >2 months of age and is considered as a treatment of choice. However, it is the most expensive of all the topical scabicides.

Oral Therapy

- Ivermectin is an effective scabicide. It suppresses conduction of nerve impulses in the nerve–muscle synapses of insects by stimulation of gamma-amino butyric acid from pre-synaptic nerve endings and enhancement of binding to post-synaptic receptors.
- Two doses of ivermectin (200 µg/kg body weight 2 weeks apart) are effective.
- The toxic effect of ivermectin after a single dose for scabies appears to be insignificant. It is relatively safe after a single dose with side effects such as headache, pruritus, pains in the joints and muscles, fever, maculopapular rash and lymphadenopathy rarely reported.
- It is contraindicated in patients with an allergy to ivermectin and CNS disorders. It is also not indicated during pregnancy, lactation and in children less than 5 years of age.

Q. Write a short note on pediculosis.

- Caused by lice infestation.
- Common in school children, homeless people and refugees.

- Diagnosis by clinical inspection for nits (eggs; look like whitish shells; found attached to the base of hair strands near the scalp), nymphs (young lice) and adult parasites; combing can help in this regard.

Head Louse (*Pediculus humanus capitis*)

- Transmission occurs person-to-person and indirectly through hats, clothes or pillow covers.
- Presents with rash and pruritus.
- Persistent infection is often associated with secondary infection of the scalp and is an important cause of impetigo.
- Because of pruritus and subsequent sleep disturbances and difficulties in concentration, infested children may perform poorly in school.

Body Louse (*Pediculus humanus corporis*)

- Transmission occurs person-to-person through infested clothes.
- A vector for epidemic typhus, relapsing fever and trench fever.

Pubic Louse (*Pthirus pubis*)

- Infests pubic hair and occasionally other hairy areas, such as eye lashes.
- Usually transmitted during sexual intercourse.
- Treatment must therefore include the patient's partner.

Treatment

- Physical removal by wet combing (every 1–3 days for at least 2 weeks) is suboptimal.
- Topical application of lindane, malathion, permethrin and spinosad. Available treatments destroy lice, but do not reliably destroy eggs. Repeat treatment for 7–10 days later is required for complete eradication. Oral ivermectin is also effective.
- Treatment of secondary bacterial infection.

Q. What are warts? Discuss their treatment.

- Warts are the cutaneous manifestations of human papillomavirus (HPV).
- Warts may exist in different forms:
  - Common warts (*verruca vulgaris*), appear as firm, irregular verrucous surfaced papules that vary in size, shape and number. These are distributed anywhere on the body and are asymptomatic.
  - Plantar warts (*verruca plantaris*) occur on the plantar aspects and are painful keratotic plaques with a central depressed area.
  - Flat or planar warts (*verruca plana*) are smooth, skin-coloured, and flat topped papules that are more frequently seen on the face or hands of children.
  - Warts located in ano-genital region are due to sexual transmission of virus and are known as venereal or genital warts. They are caused by multiple strains of human papilloma virus (HPV). They can vary from flesh-coloured to white, pink, or brown. The locations involved in women can be the cervix, vagina, vulva, urethral meatus, and perianal region. In men, the scrotum, penis shaft, corona and under the foreskin, and perianal region can be involved. *Condyloma acuminata* is a type of venereal wart that shows vegetative or cauliflower-like growth. HPV 16 and 18 are found to be most commonly associated with invasive cervical carcinoma. HPV vaccine may be offered to females after 11–12 years of age. However, cervical cancer screening is still recommended in vaccinated females.

Treatment

- No single therapy has been proven effective at achieving complete remission in every patient.
- These can be destroyed by local salicylic acid (10–20%) application, imiquimod (5% cream), cryotherapy with liquid nitrogen, chemical cauterisation (50–100% trichloroacetic acid or phenol), electric cauterisation or surgical removal.
- Sinecatechins, a mixture of 8 catechins, in the form of 15% ointment can be applied by the patient for treatment of external genital warts and perianal warts.
- Podophylline resin 25% in alcohol is effective in condyloma acuminata.
- Bleomycin injection into the wart may be used as a second-line agent if others fail.
- Systemic retinoids have the ability to alter keratinisation and accelerate clearing of warts by inducing an irritant dermatitis.

Q. Discuss the aetiology, clinical features, diagnosis and treatment of pemphigus vulgaris.

Q. What is Nikolsky's sign?

- Pemphigus vulgaris (PV) is a chronic vesicular and erosive disease characterized by intraepithelial blister formation. It may lead to systemic involvement due to fluid exudation or infection.
- PV affects both sexes equally.
- The disease is most prevalent between the fourth and sixth decades of life.
- Strongly associated with HLA-DR4 and HLA-DR6.

Aetiology

- While the precise aetiology of PV is not clear, it is known to involve an autoimmune mechanism with IgG antibodies that alter the epithelial intercellular junctions. These antibodies target desmoglein 3, and later desmoglein 1. Desmogleins belong to a subfamily of cellular adhesion molecules found within desmosomes.
- Pemphigus can also be drug-induced. Some known PV-inducing agents are sulphonamides, penicillins and antiepileptic drugs.

Clinical Features

- In most cases (75%), oral lesions are the first manifestation of the disease.

Oral Cavity

- The lesions at first comprise small asymptomatic blisters that are very thin-walled and easily rupture giving rise to painful and hemorrhagic erosions.
- While the lesions can be located anywhere within the oral cavity, they are most often found in areas subjected to friction trauma, such as cheek mucosa, tongue, palate and lower lip.
- The lesions may persist within the mouth for a number of months before progressing to the skin and other mucosal membranes (nose, pharynx, larynx, oesophagus, vulva, penis or anus).

Skin Lesions

- The primary lesion of PV is a flaccid blister filled with clear fluid that arises on normal skin or on an erythematous base.
- The blisters are fragile; therefore, intact blisters may be sparse.
- The contents soon become turbid or the blisters rupture producing painful erosions which is the most common skin presentation.
- Erosions are often large because of their tendency to extend peripherally with the shedding of the epithelium.
- Nikolsky's sign is positive—Apply pressure to the blister or rub sideways the peri-lesional skin or normal skin with a cotton swab or finger; a positive response is indicated by extension of the blister (direct Nikolsky's sign) and/or removal of epidermis in the area immediately surrounding the blister or normal skin (indirect Nikolsky's sign). It is also positive in patients with TEN, staphylococcal scalded skin syndrome, bullous impetigo and epidermolysis bullosa. This sign is usually negative in bullous pemphigoid.

Diagnosis

- Confirmation is provided by the histological biopsy study that shows the presence of intraepithelial blisters, acantholysis and acantholytic cells (Tzanck cells).
- Tzanck cells can also be demonstrated in a smear taken from the base of a blister or oral erosion. These are rounded epidermal cells with large dense nuclei, hazy or absent nucleoli, and abundant basophilic cytoplasm. Tzanck cells are also seen in chickenpox and herpes zoster vesicles.
- Direct immunofluorescence evaluation of fresh lesion specimens reveals IgG (or occasionally IgM) and complement fragments in the intercellular space.

Treatment

- Fluids and electrolytes balance, and nutritional support may be required.
- Anaesthetic mouth lozenges may reduce the pain of mild to moderate mouth ulcers.
- Antibiotics may be required to control infections.
- To inhibit production of the aggressor antibodies, moderate doses of corticosteroids via oral or intravenous route are required.
- Immunosuppressors such as azathioprine, methotrexate, cyclosporin, cyclophosphamide or mycophenolate mofetil can be used if steroids do not help.
- Rituximab, an anti-CD20 monoclonal antibody, helps in treatment-refractory pemphigus vulgaris.

Q. Define bullous pemphigoid or pemphigoid. Briefly outline its aetiology, clinical features, diagnosis and treatment.

- Bullous pemphigoid (BP) or pemphigoid is a chronic, autoimmune, subepidermal, and blistering skin disease that rarely involves mucous membranes.
- It primarily affects elderly individuals in the fifth to seventh decades of life with an average age of 65 years at onset.

Aetiology

- BP is characterized by the presence of IgG autoantibodies specific for the hemidesmosomal antigens (BP180 and BP230) present in the basement membrane.
- BP may be precipitated by ultraviolet irradiation, X-ray therapy and exposure to some drugs (furosemide, ibuprofen and other non-steroidal anti-inflammatory agents, captopril, penicillamine and antibiotics).
- It may develop shortly after vaccination, particularly in children.
- It is occasionally associated with systemic malignancies.

Clinical Features

- The patient often presents with generalised bullous lesions on erythematous or urticarial background.
- Tense bullae arise on any part of the skin surface with a predilection on the flexural areas of the skin. The bullous lesions usually have clear fluid but may also contain haemorrhagic fluid.
- Severe pruritus is present in most cases.
- Oral and ocular mucosa involvement rarely occurs, and when seen, it is of minor clinical significance.
- The bullae usually heal without scarring.
- Relapses occur less frequently than PV.
- 30-50% patients have associated with neurological diseases including major cognitive impairment, Parkinson's disease, stroke, epilepsy and multiple sclerosis.

Diagnosis

- Direct immunofluorescence studies demonstrate deposits of antibodies and complements in a linear band at the dermal–epidermal junction.
- Indirect immunofluorescence and ELISA show presence of circulating IgG-autoantibodies in the serum.

Treatment

- The most commonly used medications are anti-inflammatory agents (e.g. corticosteroids, tetracyclines, and dapsone) and if required, immunosuppressants (e.g. azathioprine, methotrexate, mycophenolate mofetil, and cyclophosphamide).

Q. What are the common dermatophytoses? Briefly describe them.

Q. What is id reaction?

- Dermatophytosis, also known as ringworm or tinea, is a chronic infection of the skin, hair or nails by dermatophytes (a group of fungi that invade the superficial layer of the epidermis and survive on the keratin of skin, hair and nails). Species of *Trichophyton*, *Microsporum* and *Epidermophyton* are called dermatophytes.

Types

- Dermatophytosis of the glabrous skin is called tinea corporis. The lesions are circinate (hence the term "ringworm"), and erythematous pruritic papules that enlarge to form a ring. The borders are irregular, raised and active. The centre is relatively normal.
- In tinea cruris, the lesions start at the apex of the groin and extend to the inner aspect of the thighs, genitalia, perineum or gluteal regions.
- Dermatophytosis of the foot is called tinea pedis (athlete's foot). This may present as fissuring of the toe webs, scaling of the plantar surfaces or vesicles around the toe webs and soles.
- Scalp dermatophytosis is known as tinea capitis. This commonly presents as circular areas of alopecia and scaling. The "kerion" type is characterized by intense inflammatory reaction. In the so-called "endothrix infection", the hair shaft breaks off at the skin surface, leaving the hairs visible as black dots on the scalp.
- Dermatophytosis of the bearded area is known as tinea barbae.
- Tinea unguium (onychomycosis) presents as white discoloured nails or thickened, and chalky crumbling nails. Subungual hyperkeratosis may be present. Risk factors for developing onychomycosis (fungi causing nail involvement) include atopy, diabetes mellitus, immunosuppression, peripheral vascular insufficiency, occlusive footwear and nail trauma.

Id Reaction

- The dermatophytid or id reaction is a diffuse hypersensitivity response to a primary dermatosis elsewhere on the body.
- Frequently occur in the setting of a dermatophytosis but may also occur with concomitant allergic contact dermatitis or superficial bacterial infection.
- Hallmark features include itching and generalised, symmetric distribution of monomorphic juicy papules (and even, sometimes, vesicles), which can last several weeks or longer.
- Treatment includes topical steroids and antihistamines.

Diagnosis

- Based on history and characteristic cutaneous findings.
- Confirmed by potassium hydroxide (KOH) microscopy, fungal culture, and skin or nail biopsy.
- Wood's lamp examination useful in confirming a hair infection with zoophilic dermatophytes (e.g. *Microsporum*) that produce blue–green fluorescence.

Treatment

- Topical therapy is effective in mild or moderately severe lesions. Seldom effective in tinea unguium and tinea capitis.
- For tinea capitis and barbae, ketoconazole cream or shampoo can be used as an adjunct. Systemic therapy is often required.
- For tinea corporis, cruris and pedis, topical therapy using clotrimazole, ketoconazole, or miconazole applied twice a day for 4 weeks.
- For distal tinea unguium, amorolfine 5%, tioconazole 28% or ciclopirox olamine 8% may be tried.
- More severe and unresponsive lesions are treated with griseofulvin 500–1000 mg daily, fluconazole 400 mg daily, itraconazole 200 mg daily or terbinafine 250 mg daily. The period of treatment is 6–12 weeks. Fluconazole can also be given in a dose of 150–300 mg once a week for 6-12 months.

Q. Write a short note on tinea versicolor or pityriasis versicolor.

- Tinea versicolor is caused by a nondermatophyte fungus, *Malassezia furfur* (also known as *Pityrosporum ovale*), which is a normal inhabitant of the skin. Infection is promoted by heat and humidity.
- The typical lesions consist of oval scaly macules, papules and patches concentrated on the chest, shoulders and back and rarely on the face. On dark skin, they appear as hypopigmented areas, while on light skin they are slightly hyper-pigmented.
- Other diseases have been associated with tinea versicolor. These include Cushing's syndrome, hyperhidrosis and altered immune status such as HIV.
- A KOH preparation from scaling lesions will demonstrate characteristic short, cigar-butt hyphae, and spores in clusters resembling spaghetti and meatballs.
- Wood's lamp shows some pigment still evident in areas of tinea versicolor; in vitiligo, there is a total loss of pigment in the affected areas.
- Treatment includes topical application of solutions containing sulphur, salicylic acid, or selenium sulphide or imidazoles (miconazole, clotrimazole, and ketoconazole) or triazoles (fluconazole and itraconazole).
  - Selenium sulphide lotion is liberally applied to affected areas of the skin for 2 weeks; each application is allowed to remain on the skin for at least 10 minutes prior to being washed off. In resistant cases, overnight application can be helpful.
  - Topical imidazole or triazole antifungals can be applied every night for 2 weeks.
- Oral therapy is also effective for tinea versicolor and is often preferred by patients because it is more convenient and less time consuming. Ketoconazole (200 mg daily for 10 days or 400 mg/day for 2 days, though less effective), fluconazole (300 mg stat and repeat after 2 weeks; or 150–300 mg weekly for 2-4 weeks) and itraconazole (200 mg daily for 7 days or 400 mg once only) are the preferred oral agents.

Q. Describe acanthosis nigricans.

- Presents with symmetric, darkened areas of skin that are thickened and described as "velvety" in texture, and located in areas of creases such as the axillae, neck and groin.
- Other locations include the face, elbows, knees and hands.

- Acanthosis nigricans can be divided into three types.
  - Type I is associated with malignant diseases, particularly gastric and lung carcinomas; may develop acutely.
  - Type II is familial, inherited as autosomal dominant and is usually apparent at birth or may develop later in childhood.
  - Type III is the most common form and is associated with obesity, insulin-resistant disorders and other endocrine disorders, including diabetes mellitus, Cushing's disease, Addison's disease, pinealoma, and hyperandrogenic and hypogonadal states. Some medications have been linked to the development of acanthosis nigricans including oral contraceptives, insulin, glucocorticoids, nicotinic acid and methyltestosterone.

Treatment

- Treat the underlying disease.
- Reduce weight in obesity-related acanthosis nigricans.
- Some patients may benefit from medications such as metformin, oral isotretinoin, topical retinoic acid, topical salicylic acid and oral fish oil.

Q. Briefly discuss the common skin malignancies.

Skin Malignancies

Common	Uncommon
- Basal cell carcinoma (most common form of skin cancer) - Squamous cell carcinoma - Bowen's disease	- Malignant melanoma - Cutaneous T cell lymphomas (e.g. mycosis fungoides) - Kaposi's sarcoma - Apocrine carcinoma of the skin - Metastatic malignancies

Basal Cell Carcinoma

- At least three times more common than squamous cell carcinoma.
- Usually occurs on sun-exposed areas of skin. Sun exposure between 10 am and 4 pm is thought to be most harmful.
- Nose is the most frequent site.
- High-risk areas for tumour recurrence include periorbital region, eyelids, nasolabial fold, post-auricular region, pinna, ear canal, forehead and scalp.
- Most characteristic presentation is the asymptomatic nodular or nodular-ulcerative lesion that has a pearly quality and contains telangiectatic vessels. Crusting and bleeding in the centre of the tumour frequently develops.
- Has a tendency to be locally destructive.

Treatment

- Basal cell carcinoma rarely metastasises, and thus, a metastatic work-up is usually not necessary.
- Options for treatment include Mohs micrographic surgery (using microscopic control to evaluate the extent of tumour invasion before surgical excision), cryosurgery, radiation therapy, electro-desiccation and curettage, and simple excision. These methods have cure rates ranging from 85 to 95%.
- Other options include topical application of imiquimod, 5-fluorouracil, intralesional interferon-α and photodynamic therapy using photosensitisers like aminolevulinic acid and its methylated ester, and methyl aminolevulinate.

Squamous Cell Carcinoma

- Also tends to occur on sun-exposed portions of the skin such as ears, lower lip and dorsal aspect of hand.
- Chronic sun damage, sites of prior burns, chronic arsenic exposure, chronic cutaneous ulcers and sites of previous X-ray therapy predisposes to the development of squamous cell carcinoma.
- Actinic keratosis, which appears as red scaly patches on areas of chronically sun-exposed skin (face and dorsal aspects of hands), is a potential precursor of squamous cell carcinoma. High-risk population to develop actinic keratosis include the elderly and people receiving immunosuppressive therapy, and psoralen plus ultraviolet A therapy and arsenic exposure. As many as 5% of actinic keratosis will evolve into locally invasive carcinoma.
- Squamous cell carcinomas are also frequently associated with human papilloma virus (HPV).

- Chronic inflammatory conditions may also result in keratinocyte transformation to squamous cell carcinoma. These conditions include chronic venous ulcers, discoid lupus erythematosus lesions, erosive lichen planus and lymphoedema.
- Squamous cell carcinoma in-situ, also known as Bowen's disease, also has invasive malignant potential. These lesions present clinically as pink, well-defined, erythematous papules and plaques anywhere on the body including the trunk, eyelids, hands, feet, face and genital area. The lesions may have scale and may bleed.
- Tumours arising in non-sun-exposed areas or those originating de novo on areas of sun-exposed skin are prognostically worse due to greater tendency to metastasise.
- Presents commonly as a red, scaling, thickened patch on sun-exposed skin. Ulceration and bleeding may occur. If not treated, it may develop into a large mass.

Management

- In squamous cell carcinoma, regional lymph nodes should be routinely examined particularly for high-risk tumours appearing on lips, ears, peri-anal and peri-genital regions, or if the tumour arises at sites of chronic ulceration, burn scars, or sites of previous radiation therapy treatment.
- The options for treatment are similar to those for basal cell carcinoma.

Malignant Melanoma

- Risk factors include sun sensitivity, white skin, fair hair, light eyes, tendency to freckle, family history of melanoma (8–12 times increased risk), dysplastic naevi and immunosuppression.
- Solar ultraviolet exposure is the most important environmental risk factor. Melanocytic naevi (moles) are also risk factors for the future development of melanoma.
- Total nevus count more than 100 naevi increases the risk for melanoma sevenfold.
- Nearly 60% present initially as superficially expanding, irregularly pigmented macule or plaque. Some present as nodular growth.
- In a patient with a pigmented lesion, important clinical features suggesting a diagnosis of malignant melanoma are ABCDE:
  - **A**symmetrical lesion.
  - **B**order irregular.
  - **C**olour irregular.
  - **D**iameter greater than 6 mm.
  - **E**levation irregular.
- Since nearly 30% of melanomas develop in pre-existing moles, a change in any naevus should be considered suspicious of malignant transformation.

Significant Changes in Melanocytic Naevus (Mole) Suggesting Development of Melanoma

- Itching	- Ulceration
- Increase in size	- Change in shape or colour
- Reduced or increased pigmentation	- Irregularity of surface or margin
- Bleeding	

- Diagnosis is by full-thickness biopsy including the underlying subcutaneous tissue and 1–2 mm clear borders. If lesion is large, incisional or punch biopsies may be performed.

Treatment

- For local disease, surgical excision is curative.
- Patients with non-ulcerated melanoma <1mm deep are unlikely to have nodal metastasis and do not require further surgical evaluation of the lymph nodes.
- Sentinel lymph nodal biopsy is important in patients diagnosed with a melanoma with intermediate thickness (1–4 mm) and clinically negative nodes. In this technique, draining lymph node is identified by injecting radioisotope adjacent to the primary tumour. The node is then identified using radioscintigraphy and then removed to look for any histological evidence of metastasis.
- Patients with metastatic tumour in the sentinel lymph node and those who have clinically evident nodal metastasis should undergo lymph node resection with post-surgical adjuvant therapy (interferon-α-2b) as an optional therapy.
- Patients with advanced melanoma may also be offered systemic therapy like interleukin 2, vemurafenib, ipilimumab, dacarbazine, temozolomide, paclitaxel, and combination therapy.

Chapter 5
Diseases of the Nervous System

Q. Discuss the signs of upper motor and lower motor neuron lesion.

Sign	Upper motor neuron	Lower motor neuron
• Weakness	• Voluntary movements are disturbed	• Paralysis of muscles supplied by that segment or nerve
• Tone	• Hypertonia (clasp–knife spasticity)	• Hypotonia
• Reflex (tendon)	• Increased, ± clonus	• Decreased or absent
• Reflex (superficial)	• Absent or decreased	• Absent or decreased
• Plantar response	• Extensor	• Flexor or absent
• Muscle nutrition	• Disuse atrophy	• Marked atrophy
• Fasciculations	• Absent	• Present
• Bilateral movements (eyes, face, jaw, neck)	• Spared	• Affected
• Reaction of degeneration	• Absent	• Present
• Nerve conduction	• Normal	• Abnormal

Q. Describe plantar reflex and extensor plantar reflex.

Q. What are the alternative methods to elicit plantar reflex?

- Plantar reflex is a superficial reflex subserved by S_1 segment of the spinal cord. It is a nociceptive reflex.
- Described in detail first by Babinski.
- The afferent fibres travel in the tibial nerve, which is a branch of the sciatic nerve, to relay in the L_5 to S_1 cord segments. The efferent fibres from the spinal cord travel back in the sciatic nerve which divides into tibial and peroneal nerves. Fibres supplying the toe flexors travel in the tibial nerve, while those supplying the toe extensors travel in the peroneal nerve to reach the foot.
- Method of elicitation.
  - Position of patient—supine with hip and knee extended (an up going toe response may not occur with knee flexed).
  - Stimulus—mildly nociceptive by gentle but firm pressure with tip of a key.
  - Site—stimulus directed on outer aspect of heel forwards towards the little toe, and on reaching the foot pad, directed transversely across metatarsal pad from the base of little toe the base of the great toe. The stimulus should stop short of the base of great toe.
- Normal response is characterised by the following:
  - Flexor—consists of flexion of great toe at metatarsophalangeal joint with adduction of other toes.

Abnormal Responses

- Absent—no response is seen.
  - Causes—thick sole, lower motor neuron or first-order sensory neuron lesions.
- **Extensor**—extension (dorsiflexion) of the great toe with or without fanning of other toes (abduction). This is called Babinski's sign. Fanning of toes without great toe extension is of little significance. The fully developed response is also accompanied by dorsiflexion of ankle and flexion of hip and knee joint and slight abduction of thigh, leading to withdrawal of leg on plantar stimulation.
  - Causes—infants and children up to 1 year of age, during deep sleep (physiological, due to immature or unmyelinated corticospinal tracts), lesions of corticospinal tract above S1 segment, deep coma, under general anaesthesia, alcohol intoxication, hypoglycaemia and postictal stage (when it is pathological).

- Never use the term "negative Babinski's sign" for a normal response; flexor plantar response being the appropriate description
- Withdrawal—in sensitive soles, voluntary withdrawal may occur resulting in difficulties of interpretation.

Physiology

- Plantar response is a spinal reflex. It is a part of spinal flexor reflex and consists of shortening of the limb upon exposure to nociceptive stimulus. With maturation of nervous system and mainly due to myelination of corticospinal tract this response is modified to typical normal response under supraspinal control. With interruption of corticospinal influence infantile pattern re-emerges.

Alternative Methods to Elicit Plantar Reflex

- The method described above is probably the most reliable method for elicitation of plantar reflex; however, at times it may fail to do so or produce an equivocal response. Other methods can then be used to elicit the response.
  - Chaddock's sign—stimulus is applied along the lateral and dorsal aspect of the foot, below the external malleolus.
  - Oppenheim's reflex—firm pressure is applied along the shin of the tibia from below the knee up to the ankle with the knuckles of the examiner's index and middle finger.
  - Gordon's sign—calf muscle is squeezed.
  - Schaefer's sign—Achilles tendon is squeezed.

Q. Discuss hemiplegia in an elderly male. Give the differential diagnosis, investigations and treatment.

- Hemiplegia is paralysis of one side of the body (hemiparesis indicates weakness of one side of body).

Causes

Onset	Cause
• **Acute**	
• Stroke	Cerebral infarct (thrombotic, embolic), intracerebral haemorrhage (hypertensive), subarachnoid haemorrhage (SAH) with intracerebral haemorrhage or ischaemia
• Trauma	Epidural haematoma, subdural haematoma, cerebral contusion
• Others	Meningitis, encephalitis, Post-seizure (Todd's paralysis), hemiplegic migraine (usually in younger patients), drug abuse (cocain, amphetamine), hypertensive encephalopathy (rare)
• **Subacute**	Cerebral metastasis, subdural haematoma, rapidly growing malignant neoplasms (malignant glioma), granulomas (tubercular, fungal), pyogenic abscesses (metastatic infection, post-traumatic), multiple sclerosis, hypoglycaemia
• **Chronic**	Slow growing neoplasms, motor neurone disease (rare)

- The most common cause of hemiplegia in elderly is cerebral infarct. Next common cause is neoplasm, either primary or metastatic. Most common primary tumour is glioblastoma whereas most common metastasis is from lung.
- Slow growing tumours and granulomas are relatively more common in younger age group.
- Spinal cord lesions rarely cause hemiplegia. Brown-Sequard lesion of cord can cause hemiplegia.

Clinical Evaluation

- Ask about onset and progression of hemiplegia; any associated symptoms related to cardiovascular or other systems.
- In thrombotic stroke, onset of hemiplegia often occurs during sleep followed by stepwise worsening over a short period; consciousness is generally preserved.
- Ask about headache, loss of consciousness, memory impairment, affection of sensory impairment and meningeal signs.
- Ask about use of oral antidiabetic drugs, insulin, or seizures before onset of hemiplegia.
- Examine for fundus, cranial nerves, sensory impairment, meningeal signs, and reflexes

Site of Lesion

• Cortical lesion	Unequal weakness in upper and lower limbs, facial involvement, cortical sensory deficit, focal seizure, other features of involvement of various lobes of brain; visual fields normal (unless occipital lobe is involved)
• Subcortical lesion	Unequal weakness of upper and lower limbs, sensory loss, visual field defects, absence of seizure and speech disturbances
• Internal capsule lesion	Dense hemiplegia with UMN facial palsy, sparing of speech, absence of seizure
• Thalamic lesion	Hemiparesis, hemianopia, hemisensory deficit, hyperpathia
• Brainstem lesion	Hemiplegia with involvement of ipsilateral cranial nerves (crossed hemiplegia)
• Spinal cord (rare)	Hemiplegia without facial involvement (in hemisection of cord above C5 level), posterior column sensory and motor loss on the side of lesion, pain and temperature loss on the opposite side, LMN type of weakness and hyperaesthesia at the level of involvement

Investigations

- Most useful initial investigation is CT scan. In acute hemiplegia, neuroimaging is required as early diagnosis and treatment are crucial in patients with acute stroke.
- A blood glucose should be done in acute or subacute hemiparesis.
- Others that are useful or maybe necessary include the following:
  - Angiogram
  - Magnetic resonance imaging (MRI) provide a more detailed view of anatomical and pathological changes, as well as enabling non-invasive imaging of intracranial vessels. Diffusion-weighted MR sequences are able to detect ischaemia within 30 minutes of onset.
  - Histopathology

Treatment

- Stroke is managed with supportive measures, antioedema measures and care of risk factors unless patient presents early when thrombolytic therapy maybe considered.
- Intracerebral haemorrhage and aneurysmal subarachnoid haemorrhage (SAH) may or may not require surgery.
- Infective conditions will require appropriate antimicrobial therapy with or without surgery (for decompression or histological diagnosis).
- Neoplasms will require surgery for decompression and radiotherapy, if they are malignant.

Q. Write a short note on apraxia.

Definition

- Disorder of learnt motor act in the absence of weakness, akinesia, incoordination, sensory loss, abnormal tone, movements disorders (e.g. tremors or chorea), intellectual deterioration or failure to comprehend commands.
- Apraxia occur in frontal and parietal lobe lesions. It appears as, if the person has forgotten to perform a motor act that he is expected to do without difficulty.

Types

- Ideomotor apraxia is the inability to carry out a motor command in the absence of motor weakness, incoordination, sensory loss or aphasia, e.g. miming the brushing of teeth, lighting a cigarette with a matchstick, etc. The person is able to carry same motor movement automatically (voluntary-automatic dissociation). This is seen with left parietal lobe lesions.
- In dressing apraxia, the person is unable to wear his dress. This is seen with right parietal lobe lesions.
- In constructional apraxia, the person is unable to copy simple diagrams or build simple blocks. This is seen with right parietal lobe lesions.
- Ideational apraxia is the inability to create a plan for a specific movement—e.g. "pick up this pen and write down your name". This is commonly associated with confusion and dementia. Seen with bilateral parietal lesions.

Q. What is agnosia? Give a brief account.

- Failure to recognise objects, persons, sounds, shapes or smells despite intact sensory, visual and auditory pathways.

Tactile Agnosia or Astereognosis

- Inability to recognise known objects, while holding in hands in the presence of intact sensory system. It occurs due to lesions of contralateral parietal lobe.

Visual Agnosia

- Inability to recognise what is seen with eyes in the presence of intact visual pathways. The person can describe the shape, colour and size without naming it. It occurs due to damage in posterior occipital or temporal lobes.

Prosopagnosia

- A type of visual agnosia with inability to identify familiar faces, sometimes even including their own. It occurs due to parieto-occipital lesions.

Q. Describe anosognosia.

- Lack of awareness of the paralysed left limb.
- Although the term anosognosia was initially used only to describe lack of awareness for left hemiplegia, it has now been used to describe the lack of subjective experience for a wide range of neurological and neuropsychological disturbances (e.g. anosognosia for visual loss, anosognosia for aphasia, anosognosia for memory loss, etc.).
- Anosognosia with hemiplegia occurs predominantly, though not exclusively, with non-dominant (right) parietal lesions.

Q. What is sensory aphasia?

- Aphasia is a loss or impairment of verbal communication which occurs as a consequence of brain dysfunction.
- Sensory aphasia denotes dysfunction in the afferent area, i.e. failure to comprehend verbal or written messages. Lesions in the dominant posterior perisylvian areas are responsible (i.e. parietal and temporal lobes). Signs consist of poor comprehension of spoken speech and inability to read though person is able to hear and see. Patient's spoken speech is fluent, and consists of inappropriate choice of words (paraphasia), and misses substantive elements. Answers given seem to be totally irrelevant, though he is verbose. Various types of sensory aphasias are:
  a. Wernicke's aphasia (repetition is defective).
  b. Transcortical sensory aphasia (repetition is preserved).

Q. What is motor aphasia?

- Motor aphasia is a disorder in the efferent area. Lesions responsible are located in the anterior perisylvian area (e.g. inferior lateral frontal lobe). Comprehension is relatively well preserved. Spoken speech is nonfluent. Word output is reduced, effortful, dysarthric and monosyllabic. Patient is able to communicate to some extent as speech is rich in substantive elements, though it lacks the usual melody. Types of motor aphasia are:
  a. Broca's aphasia (repetition is abnormal).
  b. Transcortical motor aphasia (repetition is preserved). Occurs due to damage to the dominant hemisphere outside the speech area.

Q. Discuss the normal lobar functions and their abnormalities.
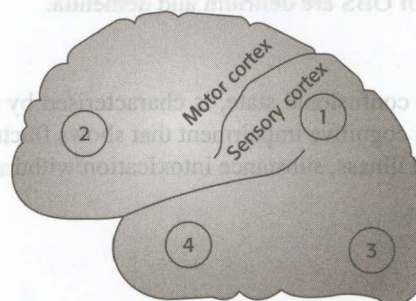
1. Parietal lobe
2. Frontal lobe
3. Occipital lobe
4. Temporal lobe

Features of Localised Cerebral Lesions

Parietal lobe			
Dominant side		**Non-dominant side**	
Function	**Lesions**	**Function**	**Lesions**
Calculation	Dyscalculia	Spatial orientation	Neglect of non-dominant
Language	Dysphasia	Constructional skills	Spatial disorientation
	Dyslexia		Constructional apraxia
Planned movement	Apraxia		Dressing apraxia
Appreciation of size, shape, weight, texture	Agnosia		Homonymous hemianopia
	Homonymous hemianopia		

Frontal lobe		Occipital lobe	
Function	**Lesions**	**Function**	**Lesions**
Personality	Disinhibition	Analysis of vision	Homonymous hemianopia
Emotional response	Lack of initiative		hemianopia scotomas
Social behaviour	Antisocial behaviour		Visual agnosia
Intelligence	Impaired memory		Impaired face recognition (prosopagnosia)
	Incontinence		
	Grasp reflexes		Visual hallucinations
	Anosmia		(lights, lines, zig-zags)

Temporal lobe			
Dominant side		**Non-dominant side**	
Function	**Lesions**	**Function**	**Lesions**
Auditory perception	Dysphasia	Auditory perception	
Speech, language	Dyslexia	Music, tone sequences	Loss of musical skills
Verbal memory	Poor memory	Nonverbal memory (faces, shapes, music)	Poor nonverbal memory
Olfaction	Complex hallucinations (smell, sound, vision)		
		Olfaction	Complex hallucinations
	Homonymous hemianopia		Homonymous hemianopia

Q. What is organic brain syndrome?

Q. Discuss briefly about delirium.

- Organic brain syndrome (OBS) is an abnormal mental state with changes in orientation, memory, judgment and affect. It results from diffuse impairment of brain tissue.
- The two most important types of OBS are delirium and dementia.

Delirium

- Delirium, also known as acute confusional state, is characterised by an acute change (usually over hours to days) in mental status along with global cognitive impairment that shows fluctuation over a period of observation.
- Often precipitated by a medical illness, substance intoxication/withdrawal or medication effect.

Common Causes

Deprivation of oxygen or energy substrate	Systemic diseases
• Hypoxia or ischaemia due to any cause	• Liver failure
• Hypoglycaemia	• Renal failure
• Wernicke's encephalopathy	• Hypercapnia
Sepsis	• Hypopituitarism
Acute poisoning	• Myxoedema
• Alcohol	• Thyrotoxicosis
• Anticholinergic agents	• Hypoparathyroidism
• Amphetamines	• Hyperparathyroidism
• Benzodiazepines	• Addison's disease
• Barbiturates	• Cushing's syndrome
• Lithium	• Diabetic hyperosmolar state
• Psychotropic drugs	• Porphyria
	• Hypoglycaemia
Acute withdrawal	• Electrolyte imbalance (sodium, magnesium, calcium)
• Alcohol	• Diabetic ketoacidosis
• Benzodiazepines	• Hypothermia or hyperthermia

Clinical Features

- It is acute in onset and is transient in course with disturbances in attention and memory.
- Deficits in attention are characterised by ease of distractibility with a reduced ability to focus, sustain or shift attention, resulting in difficulty in following commands. Patients may have trouble maintaining conversations, may repeatedly ask same questions or give different replies to same question.
- Memory impairment usually involves recent memory (e.g. forgetting about meals, medicines, visitors, etc.).
- Patients maybe disoriented to time or place but only rarely to person.
- Perceptual disturbances that may occur include misinterpretations, illusions or hallucinations (often visual hallucinations).
- Other features:
  - Agitation (e.g. try to get out of bed repeatedly, wander around in the ward, try to pull out the tubes/catheters repeatedly) or apathy.
  - Speech and language disturbances (incoherent or irrelevant speech, pressure of speech, naming things incorrectly or inability to understand what is being said)
  - Sleep disturbance (not able to sleep at night, interrupted sleep, daytime sleepiness, reversal of sleep-wake cycle).
- The features develop over a short period of time (hours to days) and tend to fluctuate during the course of the day.

Evaluation

- Review of medical and psychiatric history.
- Review of prescription and over-the-counter medications.
- Alcohol and other substance abuse history.
- Physical examination to assess systemic causes and effects.
- Evaluation of cognition by mini-mental state examination (MMSE—a 30-item instrument that includes tests of orientation, memory and concentration).
- Serum electrolytes, blood sugar, liver and kidney function tests, complete blood count, blood alcohol, thyroid-stimulating hormone, pulse oximetry and arterial blood gas.
- Cultures of blood, urine and sputum, if indicated.
- Chest radiograph, CT head and cerebrospinal fluid analysis in some patients.

Management

- Potentially life-threatening causes, including hypoxia, hypotension, hypoglycaemia, electrolyte imbalance and hyperthermia or hypothermia should be treated.
- Underlying cause of delirium should be treated.
- Supportive treatment is instituted so as to prevent any harm to the patient, while being investigated.
- If there is a potential danger of injury to the patient due to violent behaviour, physical restraints or chemicals (haloperidol 1–2 mg orally; if no response, 1–2 mg intramuscularly or intravenously; may require 5–10 mg) maybe used.
- Another agent that can be used is droperidol, which is more potent and more sedating, and has a more rapid onset and a shorter half-life than haloperidol. It can produce QTc prolongation and torsades de pointes.
- Benzodiazepines (diazepam or lorazepam) are the treatment of choice when delirium is due to alcohol, benzodiazepine or barbiturate withdrawal. Otherwise, they may produce excessive sedation.
- Atypical antidepressants (olanzapine and risperidone) are also useful and have lower incidence of side effects compared to haloperidol.
- Most patients will require admission for further management.

Q. Discuss the aetiology, clinical features, investigations and management of dementia.

Q. Describe mild cognitive impairment.

Definition

- Dementia is a global deterioration of the higher mental functions.It is characterised by problems with memory and at least one other cognitive function (learning, reasoning, language, spatial ability and orientation, and handling complex tasks) which are severe enough to interfere with activities of daily living.

Common Causes

Dementia without additional neurologic deficits	Metabolic disorders
• Alzheimer's disease	• Dialysis dementia
• Fronto temporal dementia (Pick's disease)	• Hypothyroidism
Dementia with additional neurologic deficits	• Hyperparathyroidism
• Multiple infarct dementia or vascular dementia	• Uraemia
• Parkinson's disease	• Hepatic encephalopathy
• Wilson disease	• Porphyria
• Chronic infections (tuberculosis, fungal, HIV, progressive multifocal leucoencephalopathy, syphilis)	• Vitamin B_{12} deficiency
• Hydrocephalus (obstructive and non-obstructive)	• Adrenal insufficiency
• Normal pressure hydrocephalus	• Cushing's syndrome
• Chronic subdural haematoma	• Chronic hypoglycaemia
• Lewy body dementia	**Toxic causes**
• Brain neoplasms	• Heavy metal poisoning
	• Chronic substance abuse (e.g. alcohol)

Clinical Features

- Mild cognitive impairment: Memory complaints (preferably qualified by an informant) and memory impairment relative to the patient's age and education, but preserved general cognitive function and intact activities of daily living (ADL). On MMSE, the patients generally score in the range of 26 to 28. It is the precursor to several types of dementia, including neurodegenerative (e.g. Alzheimer's disease, Parkinson's disease and dementia with Lewy bodies), vascular dementia, and dementia caused by neoplasms, normal pressure hydrocephalus and metabolic factors.
- Progression of dementia varies with the cause. Early symptoms include lapses in memory, reasoning and judgment. Mood disorders like sadness, anger and frustration are common. Gradually, deficits in all higher mental functions become evident. Dysphasia, apraxia, agnosia, urinary incontinence and focal neurological deficits occur. In later stages, deterioration in personality, personal hygiene and selfcare become evident. The person requires to be looked after by others. In advanced stages, the person is mute, lies on bed and succumbs to intercurrent infections.

Investigations

• Liver function tests	• VDRL ⎤ for syphilis	• EEG
• Renal function tests	• TPHA ⎦	• CT scan
• Endocrine evaluation	• HIV	• MRI
• Serum B$_{12}$ estimation	• CSF analysis	• PET

Treatment

• Treat the underlying cause wherever possible.

Q. Differentiation between delirium, dementia and psychosis.

Feature	Delirium	Dementia	Psychosis
• Onset	• Rapid	• Slow	• Variable
• Pattern	• Fluctuating	• Stable; occasionally fluctuating	• Stable
• Speech	• Incoherent	• Preserved	• Rapid, pressured
• Attention	• Impaired	• Normal	• Poor due to delusions
• Consciousness	• Marked fluctuation	• Clear till late stages	• Generally no impairment
• Orientation	• Disoriented	• Oriented	• Usually oriented
• Memory	• Short term impaired	• Both short and long-term memory impaired	• Selectively impaired

Q. Give a brief account of nuclear magnetic resonance (NMR) and magnetic resonance imaging (MRI).

• Magnetic resonance imaging (MRI) is an imaging technique used primarily in medical settings to produce high-quality images of the inside of the human body. MRI is based on the principles of nuclear magnetic resonance (NMR) of atoms in the tissue, a spectroscopic technique used by scientists to obtain microscopic chemical and physical information about molecules. The technique was called MRI, rather than nuclear magnetic resonance imaging (NMRI) because of the negative connotations associated with the word nuclear.

• Presently, hydrogen atom in the tissue is selected, as it is present in every tissue, though other atoms can also be chosen. Changes in the energy state are measured under the influence of powerful fixed external magnetic field with pulses of radiofrequency waves by complex techniques.

• Normally, the magnetic axes of multiple protons within tissues are randomly aligned. When surrounded by a strong magnetic field, as in an MRI machine, the magnetic axes align along the field. Application of a radiofrequency pulse causes the axes of all protons to momentarily align against the field in a highenergy state. Then the field is suddenly reduced. Some protons then relax back to their baseline state within the magnetic field. The magnitude and rate of energy release that occurs with return to baseline alignment (T_1 relaxation) and with the wobbling (precession) of protons during the process (T_2 relaxation), are recorded as spatially localised signal intensities by a coil (antenna). These intensities are used to produce images.

• Magnetic strength of MRI is measured in tesla.

• A T_1-weighted sequence accentuates substances that contain fat, while a T_2-weighted sequence accentuates substances that contain water.

• In the brain, T_1-weighted images show the nerve connections of white matter to appear white (hyperintense), and the congregations of neurons of grey matter to appear grey, while cerebrospinal fluid appears dark. This is reversed in T_2-weighted imaging.

• MRI is preferred to CT when soft tissue contrast resolution is important---e.g. to evaluate intracranial, spinal or spinal cord abnormalities, or to evaluate suspected musculoskeletal tumours, inflammation, trauma or internal joint derangement.

Contrast MRI

- The most frequently used intravenous contrast agents are based on chelates of gadolinium, which have magnetic properties that affect proton relaxation times.
- Contrast maybe used to highlight vascular structures (magnetic resonance angiography) and to help characterise inflammation and tumours.
- Can cause headache, nausea, pain and sensation of cold at the injection site, taste distortion, dizziness, vasodilation and reduced threshold for seizures. Anaphylactoid reactions are rare.
- Another rare but important complication of gadolinium is nephrogenic systemic fibrosis that involves fibrosis of dermis, joints and internal organs including lungs and heart. It usually occurs in patients with underlying chronic kidney failure; most of these patients are on dialysis. Because of this reason, gadolinium-enhanced MRI is contraindicated in patients with acute or chronic renal insufficiency, with a glomerular filtration rate <30 mL/minute/1.73 m^2.

Special Forms of MRI

- Diffusion MRI measures the movement or diffusion of extracellular water molecules. Diffusion is restricted in areas of damage from such causes as trauma, stroke or some tumours. Diffusion-weighted imaging is highly sensitive to diagnose early ischaemic stroke. It is also used to differentiate active from dormant plaques in multiple sclerosis.
- Magnetic resonance angiography is used to generate pictures of the arteries in order to evaluate them for stenosis or aneurysms. It is often used to evaluate the arteries of the neck and brain, the thoracic and abdominal aorta and the renal arteries.
- Magnetic resonance spectroscopy combines the spatially addressable nature of MRI with the spectroscopically rich information obtainable from MRI. It allows for the detection of amount and spatial distribution of various molecular compounds that are involved in the metabolism of pathologic and healthy tissue. The most important metabolites are creatine, choline, N-acetylacetate, citrate, lactate and lipids. It is used to study metabolic changes in brain tumours, strokes, seizure disorders, Alzheimer's disease, depression and other diseases affecting the brain.
- Functional MRI measures signal changes in the brain that are due to changing neural activity. It collects functional information on blood oxygenation or flow changes, perfusion or diffusion. fMRI studies are strongly recommended for the preoperative diagnostics of brain tumour patients to delineate functionally important neuronal tissue, which should be preserved during surgery.

Uses in Neurology

- Imaging section in any desired plane is possible.
- Clearly differentiates grey from white matter.
- Eliminates bone artefacts, e.g. at posterior fossa, spinal column, cranio vertebral junction, etc.
- Particularly useful in recognising demyelinating plaques and early gliomas.
- Magnetic resonance angiography is another application of magnetic resonance. The fast-flowing arterial blood does not produce any signal, while slower flowing blood in veins or distal to an arterial block or stenosis shows a signal. By varying the magnetic resonance parameters, both qualitative and quantitative data about blood flow can be assessed. This can be used to assess extracranial portion of carotid artery, intracranial major vessels and renal arteries.

Other Uses

- Cardiovascular MRI is the "gold standard" for quantifying ventricular volumes, ejection fraction and myocardial mass.

Complications

- MRI is a quite safe procedure. However, serious injuries have been described if a metal is present near by, which gets attracted to strong magnets of MRI and can act as a missile.
- Similarly, ferromagnetic metal clips used to clip an aneurysm may come off and cause bleeding.
- Implanted cardiac pacemakers are a contraindication to MRI. Other contraindications include vagus nerve stimulators, implanted cardio-defibrillators (ICD), cochlear implants and deep brain stimulators.

Advantages and Disadvantages of MRI

Advantages	Disadvantages
• No radiation exposure • Excellent differentiation of substances in the brain that cannot be differentiated on CT • Best detailed view of soft tissues of extremities • Detailed and accurate evaluation of breast cancers • Good for evaluating medullary bone	• Expensive and time-consuming • Spatial resolution not as good as CT • Requires experienced reader • Not good for evaluation of bone cortex • Less effective than CT at seeing air (lungs) or gas (as in infection or bowel perforation)

Q. What is the significance of xanthochromia in CSF analysis?

- Xanthochromia is the yellowness of CSF.
- It is always pathological. Xanthochromia is seen in the following conditions:
  - Old SAH where it is due to breakdown of haemoglobin into bilirubin.
  - Jaundice.
  - Excess protein in CSF.
  - Froin's syndrome (spinal subarachnoid block, pronounced xanthochromia and great excess of protein).

Q. List down the indications and contraindications of lumbar puncture.

Indications

Diagnostic indications	Therapeutic indications
Absolute • Meningitis • Encephalitis • SAH (if CT normal) • Guillain–Barre syndrome (GB syndrome) • Acute demyelinating diseases • Acute disseminated encephalomyelitis • Transverse myelitis (TM) • Unexplained coma • Unexplained dementia **Relative** • Multiple sclerosis • Pyrexia of unknown origin • Neurosyphilis	• Methotrexate in leukaemia • Spinal anaesthesia • Benign intracranial hypertension [to reduce intracranial pressure (ICP)]

Contraindications

• Raised ICP • Spinal deformity	• Local infections • Coagulation disorders

Q. Discuss the value of CSF analysis.

- Analysis of CSF is of diagnostic value. Disorders of central nervous system and some peripheral nervous system may-be made out by CSF examination. CSF can reflect abnormalities in nervous system as it bathes nervous system located within the skull and spinal canal. Major causes of CSF abnormalities are listed in the box below.

Physical abnormalities

• High CSF pressure	Raised ICP
• Blood stained	Traumatic puncture, SAH
• Xanthochromia	SAH, Froin's syndrome (spinal block), high serum bilirubin level
• Turbidity	Increased cellularity
• Cobweb formation	Tuberculous meningitis (TBM)

Chemical abnormalities

• Low sugar	Pyogenic, tuberculous, fungal and carcinomatous meningitis, rheumatoid arthritis
• Raised protein	Non-specific—reflects break in blood–brain barrier; occurs in inflammatory, infective, neoplastic and ischaemic disorders, GB syndrome, certain other peripheral neuropathies

Cytological abnormalities

• Increase in cell count	Inflammatory disorders
• Polymorphonuclear reaction	Acute inflammation, mainly pyogenic meningitis
• Lymphocytic reaction	Chronic infective disorders like TBM and fungal meningitis Immunological disorders like demyelinating diseases
• Other abnormal cellular elements	Carcinomatous meningitis Meningeal seedling of intracranial neoplasms

- In infections of central nervous system, pathogens can be isolated from CSF by staining techniques (Gram's stain, Ziehl–Neelsen's stain, India ink preparation, etc.) or cultures.
- Serological tests are available for many bacterial, mycobacterial and fungal infections, e.g. VDRL and TPHA in neurosyphilis.
- Oligoclonal Ig bands in multiple sclerosis (on paired samples).

Q. Discuss the formation of CSF and its functions.

- CSF is formed from mainly the choroid plexuses of lateral, third and fourth ventricles. Some may originate as tissue fluid formed in the brain substance. It leaves the ventricular system through the apertures in the roof of the fourth ventricle and flows through the cerebral and spinal subarachnoid spaces. It is returned into venous sinuses by the arachnoid villi.

Functions

- Serves as a cushion between the CNS and surrounding bones, thus protecting CNS against mechanical trauma.
- Serves as a reservoir and assists in the regulation of intracranial volume as a buffer, e.g. if brain volume or blood volume increases, the CSF volume decreases.
- Nourishment of the nervous tissue.
- Removal of products of neuronal metabolism.

Q. What is Froin's syndrome?

Q. Describe Queckenstedt's test.

- Froin's syndrome describes the CSF findings in cases of spinal subarachnoid block (below the block). CSF findings below the block are the following:
  - CSF pressure is reduced.
  - Queckenstedt's test suggests a block.
  - Physical—xanthochromic; coagulum may form.
  - Chemical—protein levels are grossly elevated, sugar levels are normal or occasionally reduced, if the cause is tuberculous meningitis (TBM).
  - Cytology—normal; increased cells, if the cause is TBM.

- Causes:
  - Total block due to any obstruction in CSF pathway in the spinal column.
  - Tumours (intraspinal).
  - Vertebral diseases with compression.
  - Chronic spinal arachnoiditis.

Queckenstedt's Test

- The test is performed by putting bilateral pressure on the jugular veins during the course of a lumbar puncture. Normally, there is a sharp rise in the pressure of spinal fluid in the lumbar region within 10–12 seconds and then a sharp fall when the pressure is released. If there is no rise in the pressure, it is a sign of blocking of the subarachnoid channels.

Q. Enumerate the causes of papilloedema.

- Papilloedema occurs due to obstruction of venous outflow along with stasis of axoplasmic flow within the optic nerve. It also occurs due to any cause that results in optic nerve head oedema (e.g. local causes).

Causes

Orbital	Intracranial
Ocular venous drainage block	*Raised ICP*
• Central retinal venous block	• Tumours
• Cavernous sinus thrombosis	• Abscesses, granulomas
	• Intracranial haemorrhage
Local lesions	• Hydrocephalus, diffuse brain oedema
• Optic neuritis	• Intracerebral haemorrhage
• Ischaemia of the nerve head	• Benign intracranial hypertension
• Toxins (methanol)	• Cerebral venous sinus thrombosis
• Infiltration of the disc by glioma, sarcoidosis	• Steroid withdrawal
and lymphoma	• Hypervitaminosis A
	• Superior vena cava obstruction
Systemic disorders affecting retinal vessels	
• Hypertension, vasculitis, chronic hypercarbia, COPD, polycythaemia	

Q. What is ptosis. List down its causes.

- Inability to open an upper eyelid.
- Occurs in IIIrd nerve palsy and Horner's syndrome (always partial).
- IIIrd nerve supplies levator palpebrae superioris, which when affected results in ptosis. Other signs of IIIrd nerve palsy will be present.
- Horner's syndrome occurs due to weakness of tarsal muscles, innervated by sympathetic nerves.

Ptosis and pupillary size

- Ptosis with a small pupil suggests Horner's syndrome
- Ptosis with a large pupil suggests IIIrd nerve palsy
- Ptosis with normal pupillary size may suggest infarction of IIIrd nerve, myasthenia gravis, myopathies or GB syndrome

Note: Pupillary fibres of IIIrd nerve are located peripherally in the optic nerve; a compressive lesion causes early loss of pupillary reflex, while ischaemic lesion causes pupillary sparing.

Causes

- All causes of Horner's syndrome.
- IIIrd nerve palsy.
  - Diabetes, multiple sclerosis, meningo-vascular syphilis, cerebral aneurysm, cavernous sinus thrombosis or infection, brainstem stroke and false localising sign in increased intracranial pressure due to brain displacements (may occur in cerebral tumour, haematoma, hydrocephalus and oedema).
  - Wernicke's encephalopathy (occurs due to vitamin B_1 deficiency).
  - Myasthenia gravis, ocular myopathies, neuroparalytic snake bites and botulism (all these conditions usually produce bilateral ptosis).

Q. Discuss the visual pathway. Illustrate the field defects produced at various levels.

- Visual sensory system begins at the retina, inner layer of which contains light sensitive receptor cells (rods and cones). The highest concentration of cones is in the central macular area, the fovea.
- As a result of the convex lens in the eye, objects located in the temporal visual field stimulate the nasal retina and those located in the superior visual field stimulate the inferior retina.
- More than 90% of retinal nerve fibres arise from the macula to form papillomacular bundle that pass to the optic nerve, taking up its central core. Lesions of this bundle (either in the retina or in the optic nerve head) produce central scotomas.
- Retinal nerve fibres temporal to the macula arc above or below form the papillomacular bundle to enter the optic disc. Lesions of these arcuate bundles produce arcuate scotomas.
- Nasal fibres pass directly to the nasal border of disc. Lesions of nasal retinal axons cause temporal field defects.
- In the optic nerve, macular fibres are in a central position with the superior retinal fibres above and the inferior retinal fibres below. Temporal and nasal fibres retain these positions within the optic nerve.
- At optic chiasma, the nasal fibres cross to other side, while temporal fibres continue on the same side. Thus, visual information from the left hemifields of both eyes continues through the visual pathway towards the right occipital cortex, while that from right hemifields towards the left occipital cortex.
- The crossed nasal fibres once joined with uncrossed temporal fibres proceed as the optic tract.
- These fibres in the optic tract then pass to the lateral geniculate nucleus of the thalamus.
- From the lateral geniculate nucleus, optic radiations pass posteriorly to the visual cortex. Nerve fibres originating from the superior retina (i.e. lower visual field) travel directly to the visual cortex through the parietal lobe while those from the inferior retina (superior visual field) pass through the temporal lobe.
- The primary visual cortex lies along the superior and inferior sides of the calcarine fissure. It contains a large macular projection area in the occipital pole.
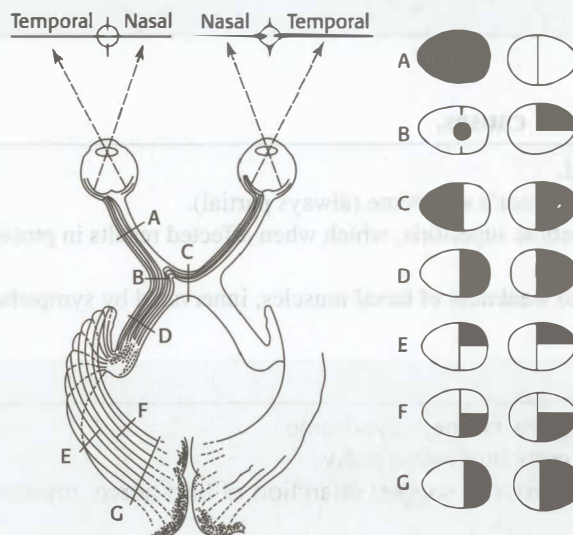
Diagram showing the effects on the fields of vision produced by lesions at various points along the optic pathway.
A. Complete blindness in left eye. B. The usual effect is a left junction scotoma in association with a right upper quadrantanopia. The latter results from interruption of right retinal nasal fibres that project into the base of the left optic nerve (Wilbrand's knee). A left nasal hemianopia could occur from a lesion of this point, but is exceedingly rare. C. Bitemporal hemianopia. D. Right homonymous hemianopia. E. and F. Right upper and lower quadrant hemianopia. G. Right homonymous hemianopia.

Visual field Defects

Central Scotoma

- Loss of vision confined to central field of vision.
- Unilateral scotoma commonly due to diseases of choroid, retina and optic nerve demyelination (as seen with multiple sclerosis) or compression.
- Bilateral scotoma due to vitamin B_{12} deficiency and alcohol.

Hemianopia

- Loss of vision in one half of the vision.
- Homonymous hemianopia: Loss of nasal field in one eye and temporal field in the other eye. Occurs due to lesion in optic tract (left optic tract lesion produces right homonymous hemianopia).
  - Incongruous hemianopia: The outline of visual filed defect in both eyes are different (e.g. lesions of optic tract or chiasma).
  - Congruous hemianopia: The outline of visual field defect in both eyes is similar (e.g. lesions of optic radiation).
- Homonymous hemianopia with macular sparing: Loss of nasal field in one eye and temporal field in the other eye with sparing of central vision in both the eyes. Occurs due to lesion in occipital cortex (lesion in left occipital cortex produces right homonymous hemianopia with macular sparing).
- Heteronymous hemianopia: Loss of either the nasal or the temporal fields in both eyes.
  - Bitemporal hemianopia: Loss of visual fields in temporal halves of both eyes. Occurs due to lesions of optic chiasma (e.g. pituitary tumours, craniopharyngioma, meningioma, hydrocephalus, aneurysm of internal carotid artery and head injury).
  - Binasal hemianopia: Loss of visual fields in the nasal parts of both eyes. Occurs due to compression of optic chiasma in the lateral aspect on both sides.
  - Upper temporal quadranopia: Loss in fields in upper quadrants of both temporal areas. Occurs due to compression of optic chiasma from below (e.g. early stage of pituitary tumours).
  - Lower temporal quadranopia: Loss of fields in bilateral lower temporal quadrants. Occurs due to compression of optic chiasma from above (e.g. early stages of distension of third ventricle).
- Quadrantic hemianopia: Upper (superior) or lower (inferior) quadrantic hemianopia indicates loss of upper or lower quadrants of visual fields, respectively. In temporal lobe lesions involvement of optic radiation causes superior quadrantic hemianopia (lesion of left anterior temporal lobe produces right upper quadrantic hemianopia). In parietal lobe lesions involvement of optic radiation causes inferior quadrantic hemianopia (lesion of left parietal lobe produces right lower quadrantic hemianopia).

Q. Give a brief account of diplopia.

- Diplopia indicates double vision.
- Uniocular or monocular (diplopia with one eye closed) and binocular (diplopia when both eyes are open).
- Uniocular diplopia occurs due to uncorrected refractory error, astigmatism, corneal opacity, corneal defect induced by laser eye surgery, lenticular opacity, ectopic lens and macular defects. If none of these is present, it indicates hysterical cause.
- Binocular diplopia occurs due to any condition resulting in loss of parallel ocular axis, e.g. IIIrd, IVth, VIth nerve palsy, internuclear ophthalmoplegia, supranuclear palsies, Grave's disease, myasthenia gravis (MG), botulism and myopathies (including thyroid-associated ophthalmopathy).
  - IIIrd nerve palsy—for causes refer above.
  - IVth nerve palsy—isolated lesion is rare (trauma); almost always associated with IIIrd or VIth nerve palsies.
  - VIth nerve palsy—carotid artery aneurysm, increased intracranial pressure diabetes, multiple sclerosis and hydrocephalus.

Internuclear Ophthalmoplegia

- Caused by a lesion of the medial longitudinal fascicle (MLF), which carries signals from the abducens nucleus to the contralateral medial rectus oculomotor subnucleus. The abducens nerve and MLF coordinate conjugate horizontal eye movements with cocontraction of ipsilateral lateral rectus and contralateral medial rectus muscles.
- Classic signs of unilateral internuclear ophthalmoplegia include impaired adduction of the ipsilesional eye and abducting nystagmus of the contralateral eye.
- Despite ipsilateral adduction weakness with direct motility testing, adduction is often intact with convergence because convergence signals to the medial rectus nucleus are distinct from the MLF.

- Smooth pursuit (slow-velocity tracking movements; elicited at bedside by having patient follow a slowly moving target) maybe normal and this condition is then diagnosed only by the presence of decreased velocity of the adducting eye during saccadic testing (high-velocity movements of varying amplitudes; elicited at bedside by having the patient rapidly shift gaze between two objects).
- Multiple sclerosis and microvascular brainstem ischaemia are the most common causes.

Supranuclear Palsies

- Result from dysfunctional cerebral, cerebellar and brainstem afferent connections to the ocular motor nuclei.
- A clinical hallmark is disproportionate involvement of saccades. Vestibular eye movements are typically spared. In contrast, nuclear and infranuclear lesions impair saccades, smooth pursuit and vestibular eye movements equally.
- Examples include progressive supranuclear palsy (a degenerative condition that initially affects vertical gaze to a greater extent than horizontal, and is accompanied by progressive dysphagia and falls) and Parinaud's syndrome (comprises supranuclear upgaze palsy, convergence nystagmus, lid retraction, and dissociation of papillary light and accommodation reflex; occurs due to pineal gland lesions and hydrocephalus).

Q. Briefly outline the clinical features and treatment of trigeminal neuralgia (Tic douloureux).

- Occurs in elderly, aetiology is unknown; maybe due to vascular compression at root entry zone of Vth nerve. This produces chronic focal demyelination that leads to increased firing rates in trigeminal primary afferents and impairment of the efficacy of the inhibitory mechanisms in the trigeminal brainstem complex.

Clinical Features

- Paroxysmal, sharp, shooting and electric shock-like pain confined to the distribution of the nerve.
- Maxillary and mandibular divisions are commonly affected. Ophthalmic division is rarely affected.
- Each paroxysm lasts only a few seconds, and maybe followed by a dull ache.
- Sometimes frequent attacks mimic pain of longer duration.
- Pain is precipitated by touching trigger zones, e.g. cold wind blowing on face, washing face, chewing or talking. Touch and vibration seems to trigger more attacks than pinprick. Trigger zones are small areas around face, nose and lips. There is often a refractory period when the pain cannot be triggered.
- A patient experiencing a trigeminal neuralgia attack typically freezes in place with hands slowly rising to the area of pain on the face but not touching it. The patient then grimaces or quirks the face in a tic (tic douloureux) and then either remains in this position or cries out in pain.
- Paroxysms are followed by remission; later, periods of remission become shorter.
- No abnormalities of Vth nerve function are seen on physical examination. Presence of sensory loss warrants investigations to exclude other conditions like multiple sclerosis, basilar artery aneurysm, etc.
- Hearing loss is absent;
- The pain of trigeminal neuralgia differs from the pain following reactivation of the varicella-zoster virus, which typically is seen in older people. When the varicella-zoster virus involves the face, it has a predilection for ophthalmic division of the trigeminal nerve.
- Trigeminal neuralgia may occur in the following conditions:
  - Multiple sclerosis (bilateral in many cases).
  - Basilar artery aneurysm.
  - Cerebral tumour, especially neurofibroma of Vth nerve or epidermoid at cerebello-pontine angle.
  - Syringobulbia.
  - Brainstem infarction.

Treatment

- Carbamazepine—start with 100–200 mg/day, increase in 2–3 weeks to 200–400 mg TID. It is the most effective drug.
- Phenytoin—100 mg TID.
- Clonazepam—1–2 mg TID.
- Lamotrigine—start with 25 mg/day, increased by 25 mg every third day, up to 400 mg a day.
- Oxcarbazepine (a keto derivative of carbamazepine)—10–20 mg/kg/day
- Gabapentin—300–900 mg TID or pregabalin 75–150 mg BID.
- Botulinum toxin type A—a non-ablative, local treatment

- Localised pain is managed with injection of phenol or alcohol into the particular branch of the nerve.
- Radiofrequency thermal rhizotomy—heat lesion of trigeminal ganglion or nerve.
- If whole nerve is involved, injection of glycerol into Gasserian ganglion.
- Gamma knife radiosurgery—using stereotactic imaging of the trigeminal nerve root entry zone, radiation is delivered to trigeminal nerve, usually 2–4 mm anterior to the brain stem.
- Sectioning of the sensory part of the Vth nerve or its descending tract in the medulla.
- Posterior cranial fossa exploration and removing compressive lesions, typical arteries or veins from trigeminal root.

Q. What are the causes of pinpoint pupil?

- Pontine haemorrhage
- Organophosphorus poisoning
- Opium poisoning
- Pilocarpine instillation
- Thalamic haemorrhage (occasionally)

Q. Write a brief note on Horner's syndrome.

- Horner's syndrome is produced by damage to the sympathetic pathway.
  - Sympathetic fibres through the IIIrd nerve innervate superior tarsal muscle of eyelid (Muller's muscles).
  - Sympathetic fibres through nasociliary nerve supply the blood vessels of eye.
  - Sympathetic fibres through long ciliary nerve innervate pupil.
- Damage to sympathetic pathway causes abnormalities in all the above-mentioned structures.

Components

- Miosis due to reduced pupillodilator activity.
- Ptosis of eyelid.
- Bloodshot conjunctiva due to loss of vasoconstrictor activity.
- Enophthalmos.
- Anhidrosis of ipsilateral half of face.
- Loss of ciliospinal reflex.

Causes

- Hemispherical lesions—hemispherectomy or massive infarction.
- Brainstem lesions—lateral medullary syndrome (vascular), multiple sclerosis, pontine glioma, brainstem encephalitis.
- Cervical cord lesions—syringomyelia, glioma, ependymoma.
- D_1 root lesions—primary and metastatic tumour of lung apex (Pancoast's tumour), cervical rib, Klumpke's paralysis.
- Sympathetic chain—neoplastic infiltration, surgery of larynx or thyroid, malignant disease near foramen lacerum or carotid canal, carotid artery dissection.
- Miscellaneous—congenital Horner's syndrome, Reider's paratrigeminal neuralgia.

Q. Discuss the aetiology, pathology, clinical features, differential diagnosis and management of Bell's palsy.

- Aetiology is not definitely known. Herpes simplex virus and herpes zoster are suspected.
- Pathologically, oedema and swelling of the nerve occur within the facial canal, often at stylomastoid foramen. Severity in a given case varies from simple conduction block to severe axonal degeneration.

Clinical Features

- Onset is acute. Sometimes history of exposure to cold is present. Mild pain at stylomastoid foramen for a few days may precede the palsy. Examination shows isolated lower motor neurone facial paralysis with or without loss of taste sensation at anterior two-third of tongue and hyperacusis.

Features of Lower Motor Facial Nerve Palsy

- Paralysis of all the muscles of facial expression on the side of palsy.
- Drooping of corner of mouth, effacement of creases and skin fold on the affected side.
- Weakness of frowning and eye closure as the upper facial muscles are weak.
- Drooling of saliva from angle of mouth.
- On asking the patient to show his teeth, the angle of mouth deviates away from the side of lesion.
- Upon attempted closure of the eyelid, the eye on the paralysed side rolls upwards (Bell's phenomenon).
- Corneal ulceration due to inability to close the eye during sleep.

Differential Diagnosis

- Herpes zoster of VIIth nerve (Ramsay Hunt syndrome).
- Middle ear disease with VIIth nerve compression.
- Trauma.
- Occasional case of intracanalicular VIIth nerve neuroma.
- Diabetic mononeuropathy.
- Upper motor neurone VIIth nerve palsy as in cerebrovascular accident (frontalis is spared, normal furrowing of the brow is preserved, and eye closure and blinking are not affected).

Investigations

- No specific confirmatory diagnostic procedure.
- Electrophysiological tests (EMG or electromyography) may help in prognostication.
- To rule out alternate diagnosis, appropriate diagnostic procedures maybe necessary.

Treatment

- If patient is seen early (within 3 days), a short course of prednisolone maybe given. Usually, prednisolone is given at 1 mg/kg/day for the 1st week, with the dosage tapering off over the 2nd week.
- Addition of acyclovir does not alter recovery.
- Adhesive tape to keep the eye closed so as to prevent corneal ulceration.

Prognosis

- Majority recovers very well (by more than 90%) if recovery starts within a few days. Poor prognosis is seen in elderly who show delayed recovery, those with hyperacusis or loss of taste sensation, and when severe axonal degeneration is suggested on electrophysiological studies. If no signs of recovery are seen at the end of 3 months, alternate diagnosis will have to be considered (VIIth nerve neuroma).
- Those who recover may show signs of anomalous reinnervation resulting in "crocodile tears", "jaw-winking", etc.

What is NOT Bell's Palsy in LMN VIIth Nerve Lesion?

• Progression at beyond 15 days	• Presence of diabetes
• Severe pain (herpes zoster)	• No evidence of any recovery at 6 months
• Any other associated neurological findings	• Bilateral facial palsy at onset
• Evidence of ear disease	

Q. Describe the aetiology, clinical features and treatment of Ramsay Hunt syndrome (geniculate herpes).

Aetiology

- Herpes zoster of geniculate ganglion.

Clinical Features

- Onset is with severe pain in external ear, followed by appearance of vesicles in the external auditory meatus, and occasionally on tongue and pharynx, along with LMN facial paralysis. Eighth nerve palsy maybe associated leading to nausea, vomiting, vertigo, nystagmus, tinnitus and hearing loss.
- Complete recovery is less likely than in Bell's palsy.

Treatment

- Analgesics.
- Oral acyclovir 800 mg five times a day is useful if started early (within 72 hours) along with corticosteroids.
- Other agents are famciclovir (500 mg three times a day) and valaciclovir (1 g three times a day).
- Idoxuridine (5% solution) maybe applied over the vesicles in early stages.

Q. Briefly outline the course of facial nerve. What are the various levels at which facial nerve can get damaged? How will you clinically differentiate between the lesions at different sites?

Site of lesion	Clinical manifestation
• Supranuclear	Contralateral upper motor neuron facial palsy and hemiparesis
• Nuclear	Ipsilateral lower motor neuron facial palsy and contralateral hemiparesis
• Cerebello-pontine angle	Ipsilateral lower motor neuron facial palsy, sensorineural deafness, loss of corneal reflex (involvement of ophthalmic division of trigeminal nerve) and ipsilateral cerebellar signs
• Internal auditory canal	Lower motor neuron facial palsy, sensorineural deafness, tinnitus or dizziness
• Tympanomastoid	Lower motor neuron facial palsy with loss of taste at anterior two-third of tongue, with or without conduction deafness and hyperacusis
• Extracranial	Lower motor neuron facial palsy with intact taste sensation
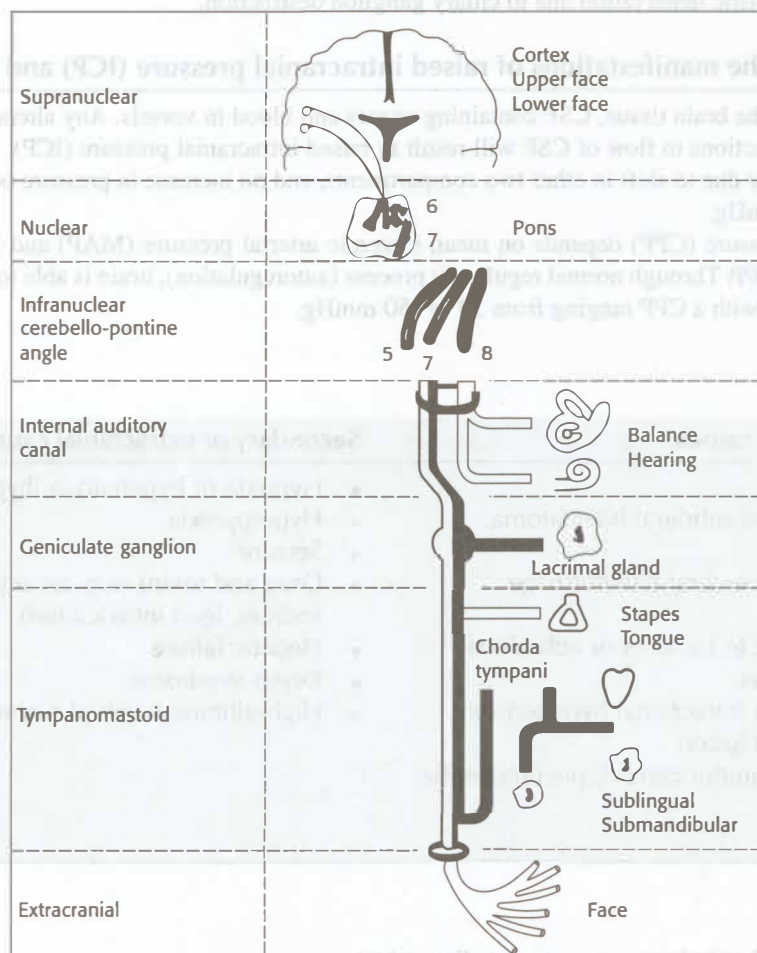
Topographical anatomy of the facial nerve

Q. Write a brief note on Argyll Robertson pupil.

- Describes the pupillary change where accommodation reflex is present but light reflex is impaired.
  - Pupils are small, irregular and unequal in size.
  - Atrophy and depigmentation of iris is seen.
  - Light reflex is absent for direct (always) and consensual (usually) stimulus.
  - Accommodation reflex is intact.
  - Ciliospinal reflex is absent.
- Tropicamide often has little or no effect on pupillary size; phenylephrine, which actively stimulates the iris dilators is often required for pupillary dilatation.
- Site of lesion is believed to be at tectum of the midbrain or peripherally in the branch of IIIrd nerve.
- Causes:
  - Neurosyphilis (mainly in tabes dorsalis)—pupillary changes generally bilateral.
  - Diabetes.
  - Sarcoidosis.
  - Multiple sclerosis.
  - Tumours of pineal region.

Q. What is Adie's pupil?

- Reaction to light is absent or greatly diminished when tested in the routine examination; however, Adie's pupil does react slowly with prolonged maximal stimulation.
- Once the Adie's pupil reacts to accommodation, the pupil tends to remain tonically constricted and dilates very slowly. Instillation of pilocarpine casues rapid constriction.
- Caused by parasympathetic denervation due to ciliary ganglion destruction.

Q. Describe briefly the manifestations of raised intracranial pressure (ICP) and its management.

- Skull encloses tightly the brain tissue, CSF containing spaces and blood in vessels. Any alteration to cause increase in tissue volume or obstructions to flow of CSF will result in raised intracranial pressure (ICP). Initially, some degree of compensation can occur due to shift in other two compartments, and no increase in pressure occurs.
- Normal ICP is <15 mmHg.
- Cerebral perfusion pressure (CPP) depends on mean systemic arterial pressure (MAP) and ICP. An increase in ICP results in decrease in CPP. Through normal regulatory process (autoregulation), brain is able to maintain a normal cerebral blood flow (CBF) with a CPP ranging from 50 to 150 mmHg.

Causes

Primary or intracranial causes	Secondary or extracranial causes
- Brain tumour - Trauma (epidural and subdural haematoma, cerebral contusion) - Non-traumatic intracerebral haemorrhage - Ischaemic stroke - Hydrocephalus (due to tumours or adhesions obstructing CSF flow) - Idiopathic or benign intracranial hypertension - Major sinus vein occlusion - Other (e.g. pseudotumour cerebri, pneumocephalus, abscess) - Post-neurosurgery	- Hypoxia or hypercarbia (hypoventilation) - Hyperpyrexia - Seizure - Drug and toxins (e.g. tetracycline, valproate sodium, lead intoxication) - Hepatic failure - Reye's syndrome - High-altitude cerebral oedema

Clinical Features

- Signs and symptoms of underlying cause are usually evident.
- Features due to raised ICP are diffuse anterior headache, vomiting and visual disturbances.
  - Headache—classically worse in mornings, exacerbated by coughing/sneezing.
  - Vomiting—typically mornings and may relieve headache temporarily

- If ICP has risen acutely, pulse rate is slower and BP maybe elevated (Cushing's reflex). Another component is respiratory depression (Cushing's triad).
- Raised ICP of more than a few days will result in papilloedema.
- Diplopia due to cranial nerve palsies—sixth cranial nerve particularly vulnerable to stretch
- Other features are drowsiness, mental deterioration and seziures.

Symptoms	Signs
Headache	Depressed level of consciousness (lethargy, stupor, coma)
Vomiting	Papilloedema
Drowsiness	Sixth cranial nerve palsy
Visual diturbances including diplopia	Cushing's triad (hypertension, bradycardia, and irregular respiration)
Seizures	

Herniation Syndromes

- Herniation of brain can occur due to raised ICT.
- Supratentorial herniations occur above the meningeal layer of the tentorium cerebelli and include central, uncal and subfalcine herniation.
- Infratentorial herniation occurs due to infratentorial lesions that may result in upward herniation of brain stem through tentorium or downward displacement of cerebellar tonsils through foramen magnum.
- Central transtentorial herniation:
  - Caused by brain swelling or an expanding space-occupying lesion that displaces medial temporal lobes along the brain stem through tentorial notch, resulting in compression and lengthening of the diencephalon.
  - Manifested as a progressive compromise of brainstem structures.
  - Initially, diencephalon is affected resulting in Cheyne–Stokes respiration, small pupils, normal oculovestibular reflexes and decorticate posture.
  - As the herniation progresses, the midbrain and upper pons are affected resulting in hyperventilation, mid-positioned and fixed pupils, abnormal oculovestibular reflex and decerebrate posture in response to noxious stimulation.
  - Further herniation leads to dysfunction of pons and medulla resulting in ataxic breathing, fixed pupils, coma and death.
- Uncal herniation:
  - Caused by an expanding mass lesion in a temporal lobe or lateral part of the cranial vault (including epidural and subdural hematomas) that forces uncus of the temporal lobe downwards and over the edge of the tentorium.
  - Initially, ipsilateral pupil dilates but remains sluggishly reactive as the outer pupillary part of the IIIrd cranial nerve is compressed.
  - Further herniation produces complete IIIrd nerve palsy, abnormal oculovestibular reflex, hyperventilation and decorticate or decerebrate posturing.
  - Ipsilateral hemiparesis may occur due to compression of the contralateral cerebral peduncle against the edge of the tentorium. It is a false localising sign (Kernohan's notch).
  - As the uncus compresses the midbrain and upper pons, hyperventilation occurs, contralateral pupil becomes fixed and dilated, and oculovestibular reflex disappears.
  - These are followed by death.
- Cerebellar herniation:
  - Causes compression of medulla resulting in altered respiration, meningismus, autonomic dysfunction, vertigo, vomiting, coma and death.

Investigations

- Relevant to possible an underlying pathology.
- CT head may show midline shift and compressed basal cisterns.
- ICP monitoring in selected cases (e.g. those with Glasgow Coma Scale ≤8 with CT scan showing haematoma, contusion, oedema, herniation or compressed basal cisterns).

Treatment

- Medical:
  - Assisted ventilation to correct hypoxia and hypercarbia. Short durations of mild hyperventilation (PCO_2 30–35 mmHg) maybe acceptable as a temporising measure until other methods of managing ICP are available. Prolonged hyperventilation has been associated with exacerbation of cerebral ischaemia.

- Maintaining mean arterial pressure above 90 mmHg. Be cautious about treating hypertension as this maybe a Cushing's response.
- Administering normal saline to achieve a central venous pressure of 8 to 10 mmHg.
- Osmotic diuretics or other diuretics:
  - Mannitol—0.25–1 g/kg/dose.
  - Glycerol—30 mL orally 6 or 8 hourly.
  - Frusemide—20 mg 8 hourly.
  - 7.5% hypertonic saline (4 mL/kg) over 15–30 minutes (with monitoring of serum sodium).
- Sedation and analgesia using short-acting benzodiazepines and morphine.
- Steroids—dexamethasone 4 mg 6 hourly. Helps only in reducing vasogenic oedema around tumour, abscess or subdural haematoma. Routine administration of steroids should be avoided in patients with traumatic brain injury and raised ICP.
- Elevation of head by 15–30°C keeping, it in midline to maximise cerebral venous drainage.
- Barbiturate coma in refractory cases. It lowers ICP by lowering the rate of the body's metabolic process, oxygen consumption and carbon dioxide production. However, its efficacy is controversial
- Cooling to about 32–34°C maybe helpful in refractory cases.
- Assisted ventilation with hyperventilation to maintain $PaCO_2$ at 30 mmHg in refractory cases (although this modality is controversial).
- Medical therapy should also include management of underlying cause wherever applicable.
- Surgical management:
  - Management of underlying cause.
  - Removal of space-occupying lesion.
  - Ventriculo-atrial or ventriculo-peritoneal shunting in hydrocephalus.
  - Decompressive craniectomy.
  - Surgical decompression as a life saving procedure by limited frontal or temporal lobectomies.

Q. Write a short note on cerebello-pontine angle (CP angle) tumours.

Q. What is acoustic neuroma?

Cerebello-Pontine Angle (CP angle)

- Cerebello-pontine (CP) angle is the area of lateral cistern containing CSF, arachnoid tissue, cranial nerves and their associated vessels. The borders of CP angle are:
  - Medial border—lateral surface of the brain stem.
  - Lateral border—petrous bone.
  - Superior border—middle cerebellar peduncle and cerebellum.
  - Inferior border—arachnoid tissue of lower cranial nerves.
  - Posterior—cerebellar peduncle.
- CP angle tumours are the most common posterior fossa tumours. Majority are benign.

Various CP Angle Tumours

• Acoustic neuroma (more than 80%)	• Cerebellar glioma
• Meningioma	• Pontine glioma
• VIIth or Vth nerve neuromas	• Nasopharyngeal tumour extension
• Epidermoid tumour	• Metastatic tumours (very rare)
• Giant basilar aneurysm	

Clinical Features of CP Angle Tumours

- Combination of VIIIth, VIIth, and ophthalmic branch of Vth, with or without ipsilateral cerebellar signs, is the hallmark of cerebello-pontine angle lesion.
- Common presenting features are ipsilateral hearing loss, tinnitus, vertigo, unsteadiness and facial hypoaesthesia. Facial weakness is uncommon.
- Tumours later will result in raised ICP by displacing brainstem and obstructing CSF flow.
- In some cases there maybe signs of brainstem compression, particularly contralateral hemiparesis.
- May result in IXth and Xth nerve palsies when tumour is very large.

Acoustic Neuroma

- Acoustic neuroma (or vestibular schwannoma) is a benign primary intracranial tumour of the myelin forming cells called "Schwann cells" of the VIIIth cranial nerve.
- May occur sporadically, or in some cases occurs as part of von Recklinghausen neurofibromatosis in which case it may take on one of the following two forms:
  - Neurofibromatosis type I occurs usually in adult life and may involve the VIIIth nerve or any other cranial nerve or the spinal root. Bilateral acoustic neuromas are rare in this type.
  - Neurofibromatosis type II usually occurs before the age of 20 years. Bilateral acoustic neuromas are the hallmark. This type shows autosomal dominant inheritance.

Investigations

- Radiograph of skull—periorbital view for internal acoustic canal or foramen.
- Brainstem auditory responses (BAER)
- CT scan (with IV contrast).
- MRI with gadolinium enhancement.

Treatment

- Surgical excision.
- Stereotactic radiosurgery (gamma knife) is used to slow down or stop the tumour growth, not to cure or remove the tumour. Often performed in elderly or sick patients who are unable to tolerate brain surgery.

Q. Mention the causes of intracranial space-occupying lesions and describe the signs and symptoms of such lesions.

Causes

Acute to subacute lesions (developing within days and weeks)	
- Subdural haematoma	
- Glioblastoma	
- Metastatic brain tumours	
- Cerebral abscess and granulomas	
Chronic lesions	
Extracerebral	*Intracerebral*
- Meningioma	- Gliomas
- Neurofibroma	- Astrocytoma
- Pituitary adenoma	- Oligodendroglioma
- Craniopharyngioma	- Glioblastoma
- Base of the skull tumours	- Haemangioma
- Pinealoma (children)	- Medulloblastoma (children)
Intraventricular	- Lymphoma
- Ependymoma	- Large aneurysms
- Colloid cyst	- Tuberculoma
- Meningioma	- Neurocysticercosis

Clinical Features

- Rapidly growing tumours produce non-localising features in the form of apathy, clouding of consciousness, global deterioration in intellect with or without features of raised ICP and seizures.
- Subacute or chronic lesions produce the following features:
  - Specific syndromes due to the lesion compressing on adjacent neural structures include the following:
    - Cerebello-pontine angle syndrome.
    - Sellar, suprasellar and parasellar syndromes (bitemporal hemianopia, scotomas, ophthalmoplegia, hypogonadism, hypothyroidism, temperature dysregulation, sleep disorders, diabetes insipidus and features of raised intracranial tension).

- Orbital fissure syndrome (proptosis, reduced acuity, pupillary changes and limited eye movements).
      - Foster–Kennedy syndrome (papilloedema in one eye and optic atrophy in the other, results from simultaneous raised ICP and optic nerve compression secondary to tumour—meningioma of the olfactory groove or sphenoid wing).
      - Intracerebral tumours result in hemiparesis, aphasia, hemianopia, cerebellar signs and brainstem signs depending on their location.
    - Features of raised ICP are headache, vomiting and papilloedema. Tumours located close to ventricular system produce early rise in ICP by blocking CSF flow even when the size of the tumour is small. Elsewhere, tumours have to be large enough to produce raised ICP.
    - False localising signs appear after raised ICP occurs. They are the following:
      - VIth nerve palsy (unilateral or bilateral).
      - Pyramidal disturbances (ipsi or contralateral side).
      - IIIrd nerve palsy.
      - Rarely, VIIth and VIIIth nerve palsy.
  - Seizures occur in supratentorial lesions.
    - Low-grade gliomas present more frequently with seizures than high-grade primary brain tumours or metastases.
    - Cortical tumours more likely cause seizures than infratentorial, deep grey or white matter lesions.
  - If the tumour is metastatic, features of primary neoplasm are evident. Common primary tumours resulting in brain metastasis are from lung, bowel, kidney, breast and thyroid.
  - If the space-occupying lesion is inflammatory, source of infection maybe evident (middle ear disease, lung abscess, bronchiectasis, abscess elsewhere in the body, cyanotic heart disease, tuberculosis elsewhere in the body, etc.).
  - Risk of deep venous thrombosis and pulmonary embolism is increased in patients with tumours.

Investigations

- Skull radiography:
  - It shows features of raised ICP at sella with shift of calcified pineal gland. Calcification within tumours maybe seen.
- CT scan:
  - It allows localisation of the tumour, its size, characters, etc., allowing identification of nature of underlying pathology in most of the cases.
- MRI:
  - Detects early gliomas and posterior fossa tumours by eliminating bone artefacts (a disadvantage with CT scan).
- Angiography:
  - Occasionally required to study the vascularity of the tumour or to rule out giant aneurysms that mimic or act as space-occupying lesions.
- Investigations to look for primary site of malignancy when metastatic tumour is suspected.
- PET scan
- SPECT scan using various tracers (e.g. 99m-Tc-glucoheptonate) to differentiate neoplastic intracranial lesions from non-neoplastic ones. Also useful to distinguish tumour recurrence from tumour necrosis that can occur with radiotherapy.

Treatment

- Seizure control.
- Control of raised ICP.
- Surgical removal to the extent possible.
- Radiotherapy is indicated in all malignant and some benign lesions.
- Chemotherapy in malignant neoplasm. Temozolomide is the most often used agent.
- Antibacterial agents in infective and inflammatory lesions.
- Prophylaxis with heparin/oral anticoagulants for patients who have lower limb immobility.

Q. Discuss the classification, pathogenesis, clinical features and management of migraine.

- Migraine is characterised by periodic headaches, typically unilateral, often associated with visual disturbance and vomiting.

Classification

Classical migraine
- Visual or sensory symptoms precede or accompany the headache

Common migraine
- No visual or sensory features
- Headache, nausea, vomiting and photophobia occur

Basilar migraine
- Occipital headache, preceded by vertigo, diplopia and dysarthria, ± visual and sensory symptoms (brain-stem symptoms)

Hemiplegic migraine
- Prolonged headache lasting hours or days
- Aura consisting of fully reversible hemiparesis and at least one of the following: fully reversible visual symptoms; fully reversible sensory symptoms; fully reversible dysphasic speech disturbance

Typical aura without headache
- Presence of migraine aura without headache (visual aura most common)

Retinal migraine
- Repeated attacks of monocular visual disturbance, including scintillations, scotomata or blindness associated with migraine headache

Pathogenesis

- Multiple environmental and genetic factors combine to induce cerebral electrical and vascular changes. Many neurotransmitters seem to be involved (e.g. serotonin, noradrenaline and substance P).
- It is initiated by spreading waves of depolarisation from either cortex or brain stem. These central processes generate meningeal neurogenic inflammation and vasodilation, which in turn activates nociceptive afferents that carry the pain signals through the trigeminal ganglion to trigeminal nucleus caudalis in the trigemino-cervical complex.
- Meningeal neurogenic inflammatory changes include the release of calcitonin gene related peptide (CGRP), a profound endogenous vasodilator and initiation of the arachidonic acid cascade.
- Aura is also thought to be caused by cortical spreading depression. Aura is associated with a localised reduction in blood flow followed by an increase in blood flow and characteristically affects the parieto-occipital cortex.

Precipitating Factors

- "Anything under the sun including sun" can precipitate an attack, but each person has his own triggering factors.
- Commonly, these are stress, exposure to bright light, loud noises, smoke or strong scents, menstruation, lack or excess of sleep, cheese, caffeine, alcohol, chocolate, citrus fruit and food additives such as monosodium glutamate, vasodilators, exercise and contraceptive pills.
- Familial tendency is usual.

Clinical Features

- Attacks are episodic and start at puberty and continue till late middle life with variable degree of spontaneous remissions. Frequency, duration and severity of attacks vary in the same individual.
- Headache is typically hemicranial, throbbing in character, and associated with nausea and vomiting.
- In classical migraine, headache is preceded by an aura that is a focal neurologic disturbance manifestating as visual aura (flashing lights or scintillating spots that may cross visual field over minutes, scotoma), sensory aura or language aura.
  - Both sensory and visual auras have a slow migratory or spreading quality in which symptoms slowly spread across the affected body part or the visual field, followed by a gradual return to normal function in the areas first affected after 20 to 60 minutes. In an ischaemic event, neurologic deficits tend to appear somewhat suddenly and tend to be equally distributed within the relevant vascular territory.

- In migraine aura, different neurologic symptoms tend to occur sequentially (e.g. visual aura followed by sensory aura). In contrast, simultaneous manifestation of multiple types of neurologic symptoms is quite common in cerebral ischaemia.
  - In migraine aura, positive features are followed by negative symptoms instead of occurring simultaneously.
- Allodynia (production of pain from normally nonpainful stimuli) is an extremely common phenomenon in migraine, occurring in about two-thirds of patients.
- Severe attacks are associated with photophobia and prostration. The attack spontaneously terminates after a few hours or sleep.

Diagnostic Criteria

Common Migraine

- Repeated attacks (at least five attacks) of headache lasting 4–72 hours that have the following features:
- Normal physical examination
- No other reasonable cause for the headache
- Headache has at least two of the following:
  - Unilateral pain
  - Throbbing or pulsatile pain
  - Aggravation of pain by movement
  - Moderate or severe intensity of pain
- At least one of the following during headache:
  - Nausea or vomiting
  - Photophobia and phonophobia

Classical Migraine

- Repeated attacks (at least two attacks) of headache lasting 4–72 hours that have the following features:
  - Normal physical examination.
  - No other reasonable cause for the headache.
  - Aura consisting of at least one of the following, but no motor weakness:
    - Fully reversible visual symptoms including positive features (e.g. flickering lights, spots or lines) and/or negative features (e.g. loss of vision)
    - Fully reversible sensory symptoms including positive features (e.g. pins and needles) and/or negative features (e.g. numbness)
    - Fully reversible dysphasic speech disturbance
    - At least two of the following:
      - Homonymous visual symptoms and/or unilateral sensory symptoms
      - At least one aura symptom developing gradually over ≥5 minutes and/or different aura symptoms occurring in succession over ≥5 minutes
      - Each symptom lasting >5 and ≤60 minutes
- Headache begins during aura or follows aura within 60 minutes

Dangerous Features of Headache in a Patient Known to Have Migraine ("Red Flags")

- Rapidly increasing frequency of headache
- Abrupt onset of severe headache
- Marked change in headache pattern
- Headache awakening the patient from sleep
- Triggered by Valsalva manoeuvre, cough, exertion or sexual activity
- Associated incoordination
- Presence of focal neurologic signs or symptoms
- Associated fever, neck stiffness
- Associated with tenderness over temporal artery
- Associated with altered sensorium, seizures

Treatment

- Explain that headache has no sinister prognosis (significance).
- Trigger factors like bright light and dietary precipitants are avoided. Keeping a headache diary can help in this regard. It may take up to 24 hours for a trigger to provoke a migraine attack.

Drugs Useful in Acute Migraine

- Initiate with an NSAID.
- Use a triptan, if no relief with an NSAID previously.
- Avoid use of opioids.
- Medication overuse headache can occur with overuse of drugs used in acute migraine.

Drug	Dose	Remarks
• **Paracetamol/Aspirin/Ibuprofen**	1 g/600 mg/600 mg	Should be initial line of treatment
• **Ketorolac**	30–60 mg IM	Non-sedating; can produce GI bleed
• **Ergotamine**	1 mg orally; can be repeated to a maximum of 3 mg/day and 5 mg/week	Use at the beginning of headache/prodrome Contraindications: Pregnancy and coronary or peripheral vascular disease Avoid if neurologic defects are present Avoid using on 2 consecutive days
• **Dihydroergotamine**	1 mg SC, IM or IV; can be repeated to a maximum of 3 mg/day and 5 mg/week	Same as ergotamine
• **Prochlorperazine**	12.5 mg IM	Effective in nearly 75% cases. Can produce extrapyramidal features
• **Metoclopramide**	10–20 mg IV slowly	Also has antiemetic properties. Can produce extrapyramidal features
• **Sumatriptan (also available in combination with naproxen)**	50–100 mg orally, 6 mg SC, 20 mg nasal spray	See below
• **Rizatriptan**	5–10 mg	See below
• **Dexamethasone**	4–8 mg IM/ IV	Non-sedating
• **Magnesium**	1 g IV	Works best for patients with aura

Triptans

- There are seven different triptans—almotriptan, eletriptan, frovatriptan (slower onset), naratriptan (slower onset), rizatriptan, sumatriptan and zolmitriptan.
- These are 5-HT1B/1D receptor agonists that work via the serotonin 1D receptors to inhibit CGRP and inflammatory peptide release in the meninges and prevent the pain signal from returning from the periphery to the trigeminal nucleus caudalis. They work via the 5-HT1B receptor to constrict vessels dilated by CGRP. Because there are some 5-HT1B receptors in coronary and other arteries, triptans are contraindicated in patients who have vascular disease.
- All triptans are available for oral use. Sumatriptan can also be given parenterally as well as by nasal spray. Zolmitriptan is also available as nasal spray.
- Should be given at the onset of headache to achieve maximum efficacy. A second dose should not be given within 2 hours if first dose is not effective.
- Side effects include tingling, flushing and sensations of warmth, heaviness, pressure or tightness in different parts of the body including the chest and neck, shortness of breath and palpitations. Triptans can constrict the coronary arteries and in rare instances may cause myocardial ischaemia.
- They are contraindicated in patients with ischaemic heart disease, uncontrolled hypertension, cerebrovascular disease, peripheral vascular disease, or hemiplegic or basilar migraine. Also contraindicated in pregnancy.
- They are compatible with most other medications. However, avoid ergotamine within 24 hours of their use.

Drug Prophylaxis

Indications

- Recurring migraine that significantly interferes with a patient's quality of life and daily routine despite acute treatment
- Four or more attacks per month
- Failure of, contraindication to, or troublesome side effects from acute medications
- Frequent, extremely long or uncomfortable auras

- Prophylaxis maybe attempted with any of the following:
  - Propranolol—40–60 mg TID, or metoprolol 25–100 mg BID, or atenolol 25–100 mg OD.
  - Pizotifen—0.5–2 mg at bed time (can produce weight gain, drowsiness).
  - Amitriptyline—25–100 mg at bed time.
  - Flunarizine—5–10 mg OD at bed time (can produce weight gain, somnolence, dry mouth, dizziness, hypotension, exacerbation of depression).
  - Gabapentin—900–3600 mg/day.
  - Valproate—400–600 mg BID.
  - Topiramate—25–100 mg BID.
  - Methysergide—1–2 mg TID in resistant cases (prolonged use may produce retroperitoneal and mediastinal fibrosis).

Q. Write a short note on cluster headache.

- Usually occurs in young adult males.
- Precise mechanism not known; cluster headache is associated with trigemino vascular activation and neuroendocrine and vegetative disturbances. Involvement of hypothalamus may explain the cyclic aspects of cluster headache.
- Familial in about 10% of cases. Having a first-degree relative with cluster headache increases the risk 14 to 40-fold
- Two types:
  - Chronic: At least one cluster period lasting at least one year, with no remission or remission of less than one month.
  - Episodic: At least two cluster periods of at least one week but less than one year, with remission for at least one month.

Clinical Features

- Characterised by recurrent, short-lasting attacks (15 to 180 minutes) of excruciating unilateral periorbital pain.
- Often accompanied by ipsilateral autonomic signs (lacrimation, nasal congestion, ptosis, miosis, lid oedema and redness of the eye).
- Circadian periodicity with attacks being clustered in bouts that can occur during specific months of the year.
- Alcohol, strong odours and napping may trigger headache.
- Attacks may happen at precise hours, especially during the night.

Diagnostic Criteria

A. At least five attacks fulfilling B through D listed below
B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15 to 180 minutes if untreated
C. Headache is accompanied by at least one of the following:
  1. Ipsilateral conjunctival injection and/or lacrimation
  2. Ipsilateral nasal congestion and/or rhinorrhea
  3. Ipsilateral eyelid oedema
  4. Ipsilateral forehead and facial sweating
  5. Ipsilateral miosis and/or ptosis
  6. A sense of restlessness or agitation
D. Attacks have a frequency from one every other day to eight per day

Treatment

- Treatment is not curative.
  - Acute treatment by sumatriptan and high flow oxygen.
  - Prophylaxis by verapamil, lithium, methysergide, prednisone, topiramate or greater occipital nerve block.
  - Deep brain stimulation in refractory cases.

Q. Classify epilepsy. Discuss the aetiology, clinical features, diagnosis and management of idiopathic epilepsy.

Q. Describe petit mal epilepsy and its treatment.

Q. What is Jacksonian epilepsy?

Classification

Focal (Partial) seizures	Primary generalised seizures	Status epilepticus

- Simple partial seizures
  - Simple partial motor seizures
  - Simple partial sensory seizures
  - Others
- Complex partial seizures
- Secondary generalised partial seizures
	- Tonic–clonic (Grand mal)
	- Tonic
	- Absence
	- Atypical absence
	- Myoclonic
	- Atonic
	- Clonic
		- Tonic–clonic status
		- Absence status (simple)
		- Focal status (complex)
		- Epilepsia partialis continua

- In focal (partial) seizures, the seizure activity starts focally in the cerebral cortex and may or may not spread to rest of the brain. In simple partial seizures, awareness is retained while in complex seizures awareness is impaired.
- In primary generalised seizures, the seizure activity appears abruptly and involves entire brain simultaneously. There is no aura. EEG shows synchronous bilateral discharges.

Definition of Epilepsy

- Brief recurrent disorder of cerebral function that is usually associated with disturbance of consciousness and accompanied by a sudden, excessive electrical discharge of cerebral neurones. EEG is of high voltage relative to the background.
- Clinically, epilepsy is defined as a condition characterised by recurrent (two or more) unprovoked seizures.

Aetiology

- Epilepsy is due to a population of abnormal hyperexcitable neurons. Such neurons are subject to excitatory and inhibitory influences from other sources. Excitatory transmitters depolarise and inhibitory transmitters hyperpolarise the neuronal membrane. The discharge is governed by the balance between these two opposing factors.
  - Acetylcholine is the excitatory transmitter.
  - GABA is the inhibitory transmitter.
- Epilepsies maybe primary or secondary (symptomatic).

Primary

- In majority of cases, epilepsy is idiopathic and the cause is not known. There maybe a positive family history, onset is in childhood and has a genetic background.

Secondary (Symptomatic)

- Any intracranial disease like cerebral tumours, head injury, cerebrovascular accidents and CNS infections.
- Hypoglycaemia and hyperglycaemia.
- Uraemia, heart block.
- Ingestion or withdrawal of alcohol or drugs.

Clinical Features

Primary Generalised Seizures

- Electrical abnormality occurs simultaneously over the entire cerebral cortex and is recognised clinically and electroencephalographically.

Tonic–Clonic Seizures

- There is an altered consciousness at the onset that maybe associated with an epileptic cry. Fit starts simultaneously with generalised tonic state that lasts for few seconds to minutes. Patient is unconscious and cyanosed, does not breathe (as glottis is closed and respiratory muscles are in tonic contraction) and pupils are dilated. Heart rate changes and may even stop. This is followed by clonic state where rhythmic jerks appear and lasts for one to few minutes. Tongue maybe bitten and urinary or bowel incontinence may occur. (Tonic state occurs during continuous discharge from the cortex when synchronous continuous excitatory activity starts. Clonic phase indicates appearance of inhibitory influence that breaks the continuous discharges to intermittent pattern).
- This is followed by postictal phase where patient passes off into sleepy state and may have headache and vomiting. At initial few minutes, he is not arousable and maybe totally flaccid. Plantar response is extensor and heart rate maybe slow. On gradual recovery he maybe confused and show automatic behaviour. Whole phase may last from a few minutes to 1–2 hours.

Absence Seizures (Petit Mal)

- Characteristic EEG pattern is synchronous generalised spike and slow wave complex occurring at a frequency of three per second.
- Three types of clinical manifestations are seen:
  1. Commonest variety (classical absence) is characterised by transient loss of consciousness. An interruption occurs in current activity and patient may stare blankly ahead. It lasts 15–20 seconds only; being so brief, may pass unnoticed. Petit mal invariably starts in childhood and may persist into adulthood. Attacks are frequent and up to 100 attacks per day maybe seen. Most often there is spontaneous remission during adulthood. However, at times, petit mal ceases and gives way to tonic–clonic seizures in adulthood.
  2. Brief loss of consciousness associated with myoclonic jerking of arms.
  3. Least common is called "akinetic seizure". Patient falls to ground, loses consciousness, recovers and rises up immediately.

Juvenile Myoclonic Epilepsy

- Juvenile myoclonic epilepsy (JME) is an idiopathic generalised epileptic syndrome characterised by myoclonic jerks, generalised tonic–clonic seizures (GTCSs) and sometimes absence seizures.
- Onset is around adolescence.
- Common precipitating factors include sleep deprivation and psychological stress.
- About 17–49% of patients have a family history of epilepsy.
- The seizures usually occur shortly after awakening.
- Myoclonic jerks occur as the only seizure type in approximately 17% of patients with JME; the rest have GTCSs (80%) or absence seizures or both.
- Patient gets bilateral, single or repetitive, arrhythmic, irregular myoclonic jerks and predominantly in the arms. Jerks may cause some patients to fall suddenly. No disturbance of consciousness is noticeable.
- Intelligence remains normal.
- Patients usually require lifelong treatment with anticonvulsants. Valproic acid or lamotrigine is useful.

Focal Seizures (Partial Seizures)

- Partial or focal seizure is a term used to describe abnormal electric activity only in a localised part of the brain.
- They maybe simple (elementary symptoms occur with no change in consciousness) or complex (symptoms at onset are complex and are associated with altered awareness of the surroundings; this does not mean that patient will lose consciousness). These attacks may terminate as focal seizures or may develop into secondary generalised tonic–clonic fits.

Simple Focal (Partial) Seizures or Focal Seizures without Impairment of Consciousness or Awareness

- Symptoms at onset maybe motor (jerking of muscles at one area, head turning), sensory (paraesthesia), visual (flashes of light), auditory (ringing sound), gustatory, olfactory or autonomic. Further symptoms depend on the spread of seizure activity.

Jacksonian Seizures

- March of symptoms occur where if it is motor, clonic jerking starts at a point, say face, and spreads to upper limb, then to lower limb and then on to opposite side to become a generalised fit. This denotes the path of spread of the epileptic activity and is called Jacksonian spread.

Complex Partial Seizures or Focal Seizures with Impairment of Consciousness or Awareness

- Complex symptoms at onset and is associated with altered awareness of the surroundings. Patients appear awake but do not meaningfully interact with people around them or respond normally to instructions or questions. Instead, patients seem to stare off into space and either remain still or demonstrate abnormal repetitive movements. Various features include the following:
  - Psychomotor (automatic, repetitive and non-purposeful behaviour such as lip smacking, chewing, walking—automatism).
  - Psychosensory (complex formed sensory hallucinations).
  - Cognitive (altered perception of reality like depersonalisation, derealisation, e.g. deja vu phenomena—the experience of feeling that one has witnessed or experienced a new situation previously).
  - Affective (change in mood, euphoria, sadness, anger, etc.).
  - Consciousness (unawareness of surroundings).
- Typically last for less than 3 minutes.
- Complex partial seizures may or may not progress to secondary generalised seizures.

Secondary Generalised Seizures

- Attack starts with an aura (which actually denotes the site of onset of seizure discharge) that maybe simple or complex, and is soon followed by loss of consciousness and generalised tonic–clonic or generalised clonic seizures. Time taken from the onset of aura to generalised seizure maybe variable but is usually very brief.
- Seizures with focal onset may have focal deficit during postictal period in the form of weakness on one side, focal sensory deficit, hemianopia, etc., which clears off over next few minutes to 1–2 hours. Presence of postictal focal deficit always suggests a focal onset of seizure activity, and invariably focal structural abnormality is recognised on further investigation. Postictal motor paralysis is called Todd's palsy.

Reflex Epilepsy

- At times, an epileptic attack maybe precipitated by a sensory stimulus and maybe easily reproduced. Common examples are the following:
  - Television epilepsy (occurs while watching television at close quarters).
  - Musicogenic (certain musical tones bring about the attack).
  - Eating.
  - Hot water (pouring hot water only over vertex).

Diagnosis of Epilepsy

- Attempt should be made to find out:
  - Whether an attack is really an epileptic fit or some other brief disorder of consciousness or disorder of CNS, e.g. syncope, migraine, transient ischaemic attack, psychogenic non-epileptic seizures, etc.
    - Differentiation of seizure from syncope is given below.

Feature	Seizure	Syncope
• Circumstances	None	Prolonged standing, alcohol, heat, pain, cough, micturition
• Aura/prodrome	Variable	Visual blurring, tinnitus, nausea, dizziness, pallor, sweating
• Duration	1–5 minutes	10–30 seconds
• Muscle tone	Usually hypertonic	Hypotonic
• Motor features	Tonic/clonic, focal progressing to generalised movements	Myoclonic/clonic jerks maybe present
• Tongue bite	Frequent	Rare
• Urine/faecal incontinence	Common	Uncommon
• Cardiovascular	Tachycardia	Bradycardia and hypotension
• Postictal confusion	Lasts for >1 minute	Lasts for a few seconds
• Postictal headache	Common, maybe severe	Uncommon, short lasting

– Psychogenic non-epileptic seizure—an observable abrupt paroxysmal change in behaviour or consciousness that resembles an epileptic seizure, but that is not accompanied by electrophysiological changes that accompany an epileptic seizure or clinical evidence of epilepsy, for which no other evidence is found for other somatic causes of the seizures, whereas there is positive evidence or a strong suspicion for psychogenic factors that may have caused the seizure.

- Type of fit—primary generalised, focal or secondary generalised (presence of aura, change in consciousness and details of the fit by a reliable observer).
- Cause of epilepsy (primary or symptomatic) by type of fit, age of onset, family history, presence or absence of neurological deficit, systemic abnormalities and by laboratory investigations, as and when necessary.

Role of EEG

- Helps in differentiating primary generalised attacks from focal epilepsies.
- Confirms the clinical diagnosis (by showing spikes and sharp waves), but normal record may occur in about 60% cases with one seizure and 40% cases with established epilepsy. If first EEG is normal, it should be repeated with the patient sleep deprived, although the test may still be normal.
- Video EEG: Prolonged EEG-video monitoring provides information about electrographic seizures and seizure activity (actual events recorded on video). It helps in making a definitive diagnosis of epilepsy.
- Ambulatory EEG is analogous to Holter monitor for cardiac arrhythmias. However, unlike video EEG, it does not permit correlation between electrographic seizures with actual events.
- A portable EEG can be done in patients with convulsive status epilepticus who do not regain consciousness as expected, so as to exclude an ongoing non-convulsive status epilepticus.

Determining the Cause of Epilepsy

- Any person having fit with focal onset or a fit starting for the first time after the age of 25 years (late onset) should be investigated for symptomatic epilepsy.
- Causes of seizures vary according to age.

Infancy
- Anoxia (or post-anoxic)
- Hypocalcaemia
- Hypoglycaemia
- Hyponatraemia
- Fever (febrile seizures)
- Meningitis, birth trauma

Early childhood
- Genetically determined metabolic disorders of brain
- CNS infections
- Idiopathic

Late childhood and adolescence
- Idiopathic (genetically determined)
- Sequelae of previous injury
- Infections
- Drugs and toxins including lead poisoning

Adult life
- Tumours
- Current or previous brain injury (traumatic or post-operative)
- CNS infections, including HIV
- Metabolic
- Drugs and toxins (cocaine, amphetamines, theophylline, alcohol, organophosphates); alcohol or benzodiazepine withdrawal
- Idiopathic

Late life
- Metabolic
- Tumours
- Current or previous brain injury (traumatic or post-surgical)
- Ischaemia to the brain
- Drugs and toxins

- Procedures:
  - CSF examination (if an infection is suspected).
  - Metabolic parameters like blood sugar, sodium, calcium, urea, creatinine, acid–base balance and magnesium.
- Neuroimaging:
  - Required in almost all cases of epilepsy unless a cause is obvious.
  - MRI is superior to CT scan for the detection of cerebral lesions associated with epilepsy.
  - When an acute intracranial pathology is suspected, an emergency CT scan is recommended. Common indications for emergency CT scan are listed in the box.

- Age over 40 years
- Partial onset seizure
- Persistent altered mental status or headache postictally
- Presence of fever
- History of recent trauma
- History of cancer
- History of anticoagulation
- Immunodeficiency
- Focal deficits on examination

- Use of newer MRI methods (e.g. FLAIR—fluid-attenuated inversions recovery) has increased the sensitivity for detection of abnormalities of cortical area.
- Functional imaging procedures such as PET and single-photon emission computed tomography (SPECT) are useful in the evaluation of patients who are refractory to medical treatment.

Treatment

- A first seizure provoked by an acute brain disturbance is unlikely to recur (3–10%), whereas a first unprovoked seizure has a recurrence risk of 30–50% over the next 2 years.
- A first seizure mandates individual counselling about the risk of recurrence, pros and cons of the drug treatment and the impact on lifestyle.

General

- Tide over the stigma by proper explanation.
- Children not to cycle on public roads.
- No swimming.
- Adopt an occupation at which neither the patient nor society is put to risk.
- Avoid exposure to moving machinery and working at heights.
- Driving only as per regulations (free of attacks for 2 years).
- Adequate sleep.
- Avoid hyperpyrexia, flickering lights and emotional disturbances.

During a Fit

- Protect from injury by moving the patient away from fire, sharp and hard objects.
- Padded gag inserted within teeth.

Antiepileptic Drugs for Chronic Use

- In general, for partial epilepsies, carbamazepine (alternatives oxcarbazepine and lamotrigine) is recommended initially, whereas for generalised epilepsies, the first-line choice is usually valproate (alternatives lamotrigine, topiramate or levetiracetam).
- Phenytoin is no longer widely used because of long-term toxicity concerns, but retains a place in terms of the ease of once daily usage and low cost.
- The new antiepileptic agents include lamotrigine, gabapentin, topiramate, tiagabine, levetiracetam, oxcarbazepine, vigabatrin and pregabalin. These are effective for partial epilepsies and some (particularly lamotrigine, topiramate and perhaps levetiracetam) are also effective in generalised epilepsies. However, in new-onset patients, none have been shown to be superior to the "older" drugs in terms of efficacy. Broadly, the newer agents have advantages of lower risk of side effects, less drug interactions and less enzyme induction. Because of their higher cost these are advised as second-line agents.
- General instructions:
  - Better to use one drug rather than combination.
  - If no control is obtained with maximum doses of first drug, a second first-line drug is initiated and the first drug is tapered. If partial control is achieved then a second drug should be added.

- If single drug does not control, at least three single drugs should be tried before combination.
- Phenytoin maybe combined with phenobarbital or carbamazepine.
- Primidone and phenobarbital should not be given together because primidone is partially converted to phenobarbital.
- Therapeutic drug monitoring is useful in only few situations, including breakthrough or refractory seizures, to assess compliance, for diagnosis of clinical toxicity or with use of phenytoin, which has dose-dependent pharmacokinetics.
- Osteomalacia and osteoporosis may occur with chronic use of phenobarbital, primidone, phenytoin and carbamazepine.
- Folic acid deficiency may occur due to phenytoin, carbamazepine, phenobarbital, primidone, oxcarbazepine and lamotrigine.
- Phenobarbital, primidone, phenytoin and carbamazepine induce metabolism of lipid-soluble drugs, such as the combined oral contraceptive pill, cytotoxic agents, antiretrovirals, statins, warfarin and antiarrhythmics.
- Primidone and phenobarbital can cause the following:
  - Drowsiness
  - Ataxia
  - Decreased libido
  - Depression
  - Skin rashes
  - Rickets
  - Osteomalacia
  - Folate deficiency leading to megaloblastic anaemia
  - Fibrosing disorders such as reflex sympathetic dystrophy, shoulder-hand syndrome, frozen shoulder and Dupuytren's contracture
  - Teratogenic effect
- Phenytoin can cause the following:
  - Drowsiness and ataxia
  - Rickets
  - Osteomalacia
  - Folate deficiency leading to megaloblastic anaemia
  - Teratogenic effect
  - Gingival hyperplasia
  - Coarsening of features, hirsutism
  - Lymphadenopathy
  - Syndrome mimicking systemic lupus erythematosus
- Valproate can produce weight gain, tremors, hair loss and thrombocytopenia.
- Carbamazepine can produce the following side effects:
  - Ataxia
  - Dizziness
  - Diplopia
  - Vertigo
  - Hyponatraemia
  - Bone marrow suppression
  - Hepatotoxicity
  - GI irritation
  - Stevens–Johnson syndrome
- Teratogenic effect is maximum with phenytoin (foetal hydantoin syndrome—mental retardation, craniofacial anomalies including microcephaly, growth retardation, hypoplasia of distal phalanx of fingers and toes, nail hypoplasia, cleft-lip/palate and rib anomalies) and valproate (foetal valproate syndrome—central nervous system dysfunction, spina bifida, development delay, intrauterine growth retardation and cardiac anomalies). Carbamazepine is the safest drug in females of reproductive years, though it also produces teratogenicity.
- Antiepileptic therapy can gradually be withdrawn if patient is totally seizure free for 3–5 years depending on the seizure type, age of the patient and previous seizure control.

Treatment of Various Types of Epilepsies

Type of epilepsy	First-line drugs	Alternative drugs
• **Primary generalised tonic–clonic epilepsy**	Valproic acid (400–3000 mg/day in two to three divided doses) Phenytoin (200–400 mg/day as single dose) Carbamazepine (600–1800 mg/day in two to three divided doses)	Phenobarbital (60–180 mg/day as single dose) Lamotrigine (150–500 mg/day in two divided doses) Topiramate (400 mg/day in two divided doses) Felbamate (2400–3600 mg/day in three to four divided doses)
• **Partial epilepsy**	Carbamazepine Phenytoin Oxcarbazepine (0.6–2.4 g/day in 2–4 divided doses) Lamotrigine Levetiracetam (in elderly)	Phenobarbital Gabapentin (as adjunct; 900–2400 mg/day in three divided doses) Topiramate (as adjunct; 400 mg/day in two divided doses)
• **Absence epilepsy**	Ethosuximide (750–1250 mg/day as single dose) Valproic acid	Lamotrigine Clonazepam (1–12 mg/day in one to three divided doses)
• **Atypical absence, myoclonic and atonic epilepsy**	Valproic acid	Lamotrigine Clonazepam Topiramate (as adjunct)

Newer Antiepileptic Agents

Drug	Side effects	Dose
• Felbamate	Substantial risk for aplastic anaemia or liver failure, drowsiness, headache, nausea, constipation	1.2–3.6 g/day (in 3–4 divided doses)
• Gabapentin	Dizziness, ataxia, somnolence, GI irritation	0.9–2.4 g/day (in 3 divided doses)
• Lamotrigine	Headache, dizziness, ataxia, skin rash, GI irritation, hepatotoxicity, Stevens–Johnson syndrome	Monotherapy 300–500 mg/day With valproic acid: 100–150 mg/day
• Levetiracetam	Somnolence, incoordination, irritability, mood swings, psychosis	1–3 g/day (in 2 divided doses)
• Oxcarbazepine	Ataxia, dizziness, diplopia, blurred vision, vertigo, rash, bone marrow depression, GI irritation, hepatotoxicity, hyponatraemia	0.6–2.4 g/day (in 2–4 divided doses)
• Pregabalin	Drowsiness, dizziness, oedema, impaired concentration, blurred vision, weight gain, ataxia	150–600 mg/day (in 2 divided doses)
• Tiagabine	Somnolence, paraesthesia, psychosis, tremors	Without enzyme-inducing drugs 15–30 mg/day (in 2–4 divided doses)
• Topiramate	Somnolence, speech problem, paraesthesia, weight loss, renal calculus, metabolic acidosis, angle-closure glaucoma	With enzyme-inducing drugs 30–45 mg/day 200–400 mg/day (in 2 divided doses)
• Vigabatrin	Headache, drowsiness, skin rash, constipation, depression, weight gain	Maximum 800 mg/day 2–3 g/day (maximum 3 g/day)

Surgery

- Surgical treatment is an option for epilepsy when an underlying brain abnormality such as where a benign tumour can be identified and removed.
- In other cases, surgery is usually only offered when epilepsy has not been controlled by adequate attempts with multiple medications.
- The most common form of resective surgical treatment for epilepsy is to remove the front part of either the right or left temporal lobe.
- Palliative surgery for epilepsy is intended to reduce the frequency or severity of seizures. Examples are callosotomy or commissurotomy to prevent seizures from generalising.
- Hemispherectomy is a drastic operation in which most or all of one-half of the cerebral cortex is removed. It is reserved for people suffering from the most catastrophic epilepsies.

Miscellaneous

- Direct brain stimulation has been shown to be effective in some cases.
- Ketogenic diet—a stringently controlled high-fat and low-protein/carbohydrate diet given with/without a restricted fluid intake to maintain ketosis on a long-term basis—in refractory cases where surgery cannot be performed. Adverse effects include GI disturbances, acidosis, increased susceptibility to infections, drowsiness, weight loss and nutritional deficiencies.

Q. What is status epilepticus? How will you manage a case of status epilepticus?

- Status epilepticus denotes sustained epileptic activity, and is clinically diagnosed with one of the following two:
- Two fits occur without recovery of consciousness in between.
- A single fit lasts longer than 30 minutes with or without loss of consciousness.
- However, most physicians define status epilepticus as either convulsion lasting for more than 5 minutes (as patients with seizures that last more than 5 minutes are not likely to improve spontaneously) or when two seizures occur between which there is incomplete recovery of consciousness.
- Condition is fatal or results in severe morbidity if not treated rapidly.

Classification

- Status epilepticus can be classified into: partial and generalised.
- Generalised status epilepticus is further divided into: convulsive status epilepticus (tonic-clonic being the commonest) and non-convulsive status epilepticus (characterised by slowness in behaviour and mentation, confusion and sometimes stupor, and accompanied by generalised epileptic discharges). The latter includes absence or petit mal status.
- Partial status epilepticus includes partial motor status (associated with characteristic march of motor symptoms), partial sensory status, complex partial status and epilepsia partialis continua (focal motor seizures without a march).

Causes

- Sudden antiepileptic withdrawal
- Metabolic disorders—hypoglycaemia and hyponatraemia
- Alcohol or benzodiazepine withdrawal
- Infections—encephalitis and meningitis
- Occasionally, brain tumour or trauma

Treatment

- Priority should be to control seizures as fast as possible, along with identification of an underlying cause and its correction.

Step A (First 20 Minutes)

- Maintain airway.
- Secure a proper IV line, and draw blood for metabolic parameters. Check for blood sugar on bedside.
- Elicit a brief history from the relatives about any previous seizures, diabetes, hypertension, drug exposure or withdrawal, and head injury.
- Conduct a rapid examination to determine presence of focal signs, obvious medical illness, increased intracranial tension and associated injuries.
- Simultaneously, administer diazepam (10–20 mg IV over 1–2 minutes, maybe repeated every 10 minutes) or lorazepam (2–4 mg IV over 2 minutes) followed by loading dose of phenytoin (18–20 mg/kg) at a rate of not more than 50 mg/minute in adults and 25 mg/minute in children. Otherwise, hypotension or bradyarrhythmia may occur. Total

dose should not exceed 1000 mg. An alternate agent is fosphenytoin, which is a prodrug of phenytoin and can be given at a rate three times the phenytoin. This should control seizures in 20 minutes; if *no*,

Step B (20–60 Minutes)

- Phenobarbital (20 mg/kg IV at a rate of 50 mg/minute) or diazepam infusion (2–4 mg/hour in adults). Both may require assisted ventilation.
- Since use of phenobarbital is associated with serious adverse reactions, alternatives include valproic acid and levetiracetam.
- Valproic acid is given in a dose of 30 mg/kg over 2–5 minutes, followed by infusion at 1–5 mg/kg/hour. Another 10 mg/kg maybe given 10 minutes after initial dose. Adverse effects include hypotension, dizziness, thrombocytopenia and rarely, valproic acid encephalopathy.
- Levetiracetam is given in a dose of 2–3 g over 15 minutes.
- *If not controlled, go to step C.*

Step C

- General anaesthesia or thiopental infusion is tried. Other drugs include midazolam and propofol.
  - Midazolam—0.1–0.2 mg/kg loading followed by 0.1–2.0 mg/kg/hour.
  - Propofol—1–2 mg/kg loading followed by 1–10 mg/kg/hour.
  - Thiopental—5–7 mg/kg IV followed by 50 mg boluses every 2–3 minutes till seizure control and then 3–5 mg/kg/hour.
- Simultaneously, BP, acidosis, ventilation and electrolyte balance are taken care of. Underlying cause should be rectified appropriately.
- Aim should be to control seizures within 1 hour after admission. Otherwise, chances of residual morbidity or mortality rise steeply as duration of status gets prolonged.

Management of Convulsive Status Epilepticus

Minutes of arrival	Action
- 0–5	- Maintain airway, breathing and circulation - Administer oxygen - Insert an IV line - Obtain blood samples for glucose, urea, electrolytes, bilirubin, haemogram, acid–base analysis, toxicology screen - Administer glucose (and thiamine) if hypoglycaemic - Elicit brief history and conduct brief examination
- 5–10	- Administer diazepam or lorazepam
- 5–20	- Administer phenytoin or fosphenytoin - Repeat diazepam if seizures persist - Evaluate for intubation
- 20–60	- Administer phenobarbital - Support of respiration often required - Conduct detailed examination
- >60	- Intubate and ventilate (if not done before) - Administer general anaesthetic agents (midazolam, propofol, thiopental) with EEG monitoring - Admit in intensive care unit

Q. Give a very brief account of fosphenytoin.

- It is a prodrug of phenytoin that gets converted into phenytoin following intravenous administration. A dose of 1.5 mg of fosphenytoin is equivalent to 1 mg of phenytoin.
- Used in status epilepticus.
- Dose is 15–20 mg PE/kg at 100–150 mg/minute (where PE is phenytoin equivalent).
- Risk of hypotension is less compared to phenytoin.

Q. Describe the circle of Willis. What are the common sites of aneurysm formation?
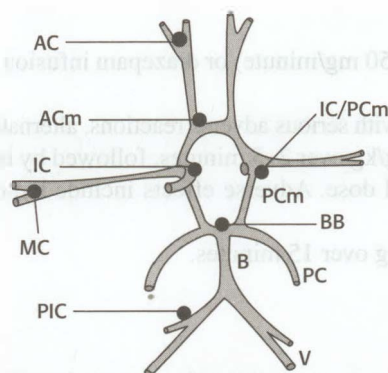
Arteries contributing to the circle of Willis, their major branches and the commonest sites of aneurysm

AC = Anterior cerebral artery. ACm = Anterior communicating artery. B = Basilar artery. BB = Basilar bifurcation. IC = Internal carotid artery. IC/PCm = Internal carotid/Posterior communicating artery. MC = Middle cerebral artery. PC = Posterior cerebral artery. PCm = Posterior communicating artery. PIC = Posterior inferior cerebellar artery. V = Vertebral artery.

- The circle of Willis is supplied by two internal carotid arteries and basilar artery formed by joining of two vertebral arteries.
- This anastomotic pathway is crucial to preservation of brain function in the event of a major flow disruption in one of the major feeding vessels. As a result, most of the stroke syndromes occur from occlusion distal to the circle of Willis or in areas that receive blood supply from arteries that originate prior to the connection with the circle.
- Patency of communicating arteries is variable and is based on developmental and degenerative changes in a particular individual.

Q. Give an account of different types of cerebrovascular accidents and their pathophysiology.

- Cerebrovascular accident or stroke is defined as abrupt onset neurological disorder of vascular aetiology.
- Strokes maybe haemorrhagic or ischaemic in nature.
- Ischaemic strokes can be due to embolism or thrombosis.

Types of Haemorrhagic Strokes

- Primary intracerebral haemorrhage
- Subarachnoid haemorrhage
- Primary intraventricular haemorrhage

Types of Ischaemic Strokes

- Transient ischaemic attacks (TIA)
- Completed stroke
- Lacunar infarcts
- Watershed infarcts, also known as border zone infarcts, develop from relative hypoperfusion in the most distal arterial territories and can produce bilateral symptoms. Frequently, these occur perioperatively or in situations of prolonged hypotension.
- In addition to these, multifocal small infarcts or ischaemia may result in slowly progressive neurological disorders, causing multi-infarct dementia and subcortical arteriosclerotic encephalopathy (Binswanger's disease).

Pathophysiology

- The two main developments an underlying therapeutic advances in stroke are the delineation of the ischaemic penumbra in ischaemic stroke and the observation of haematoma growth in intracerebral haemorrhage.

Ischaemic Stroke

- The severity of an acute ischaemic stroke depends on the degree of impairment of cerebral blood flow (CBF) and the time to reperfusion. As the ischaemic process evolves, most commonly due to thromboembolic arterial occlusion, there

- is a progressive decrease in CBF. When it falls from normal levels of approximately 50 to <10 mL/100 g brain tissue/minute, neuronal cell death occurs rapidly.
- However, between the ischaemic core and the normally perfused brain at the periphery lies the ischaemic penumbra, a zone of moderately reduced CBF, dependent on the proximal arterial occlusion and collateral supply.
- Within the ischaemic penumbra, the neurons are hypoxic, functionally inactive, but still viable. In the penumbra, the brain tissue will undergo necrosis over hours to days due to perfusion failure, and a secondary cascade of damaging biochemical events. These neurotoxic processes include release of glutamate, activation of N-methyl-D-aspartate (NMDA) and other cell receptors, influx of sodium and calcium into cells, release of free radical species and ultimately cellular destruction.
- A limited therapeutic window of opportunity underlies the concept that "time is brain".

Intracerebral Haemorrhage

- ICH is also a dynamic process and substantial haematoma growth (greater than one-third increase in volume) can occur within first 3 hours with most of the growth in the first 1 hour. This expansion is probably due to continued bleeding or rebleeding. Haematoma expansion is an important cause of early neurological deterioration, the severity of which depends on original haematoma size and subsequent expansion rate. This observation is the basis of giving haemostatic therapy in ICH that could reduce the volume of the haematoma and possibly result in improved outcomes.
- Another cause of deterioration is development of perihaematoma brain oedema that may evolve over many days. It is the primary cause of neurological deterioration after the first day of bleed. Perihaemorrhagic tissue damage is primarily related to the inflammatory and cytotoxic response and not due to ischaemia produced by oedema.

Q. What are the risk factors for stroke?

Risk factors in patients of all age groups	Additional risk factors that are more common in young patients
High risk	• Protein C and S deficiencies
• Hypertension (including isolated systolic)	• Antithrombin III deficiency
• Diabetes mellitus	• Antiphospholipid syndrome
• Atrial fibrillation with or without valvular heart disease	• Factor V Leiden
	• Sickle cell anaemia
• Smoking	• Hyperhomocysteinaemia
• Use of cocaine or amphetamines	• Thrombotic thrombocytopenic purpura
• Vasculitis (polyarteritis nodosa, Wegener's, Takayasu's arteritis, primary CNS vasculitis, vasculitis related to meningitis)	• Arterial dissection
	• Infections (e.g. syphilis, HIV)
• Dilated cardiomyopathy	
• Endocarditis	
Low risk	
• Migraine	
• Use of oral contraceptives or alcohol	
• Patent foramen ovale	
• Recent myocardial infarction	
• Prosthetic valve	

Q. Define transient ischaemic attacks (TIA). Discuss its mechanism, clinical features, investigations and management.

Definition

- Abrupt onset focal neurological deficit of presumed vascular aetiology not lasting longer than 24 hours. Many episodes last for a few seconds to minutes and rarely up to 24 hours. Defining TIA with a 24 hour maximum duration has the potential to delay the initiation of effective stroke therapies.
- A more recent definition of TIA is a brief episode of neurological dysfunction caused by focal brain or retinal ischaemia without neuroimaging evidence of acute infarction. Therefore, without diagnostic imaging it is not possible

to make a distinction between TIA and stroke. This definition underscores the urgency of recognizing TIA as an important warning of impending stroke and facilitating rapid evaluation and treatment of TIA to prevent permanent brain ischaemia. There is no reliable way to determine, if the abrupt onset of neurologic deficits represents reversible ischaemia without subsequent brain damage or if ischaemia will result in permanent damage to the brain (e.g. stroke).

Mechanism

- Various causes of TIAs are given in the box below

Mechanism	Common examples
Large artery atherosclerosis	Carotid stenosis, vertebrobasilar disease, aortic atherosclerosis
Cardioaortic embolism	Atrial fibrillation, valvular disease, left ventricle thrombus
Small artery occlusion	Intracranial small-vessel disease from long-standing hypertension, intracranial atherosclerosis
Others	Arterial dissection, hypercoagulable states

- Usually, TIAs occur due to a platelet thrombus getting dislodged from an atherosclerotic plaque to cause short-lasting obstruction at a distal branch. Embolus gets broken down resulting in re-establishment of perfusion with clearance of neurological deficit.

Symptoms and Signs

- Most TIAs resolve in less than 30 minutes. If symptoms of cerebral ischaemia do not resolve by 1 hour rapidly improve within 3 hours, complete resolution is rare,
- TIA implies an active plaque in the major feeding artery and is a warning sign of a major stroke. The risk of recurrence and stroke is about 10% within first 7 days of a TIA, with most of them occurring within 48 hours. More than 30% of patients with recurrent TIAs will suffer from completed stroke if untreated.
- Five risk factors are independently associated with a higher 3-month risk of recurrent stroke: age >60 years, symptom duration >10 minutes, weakness, speech impairment and diabetes mellitus.

Carotid Territory

- Ipsilateral mono-ocular blindness (amaurosis fugax), contralateral hemiparesis, hemianaesthesia, dysarthria and rarely hemianopia, monoparesis, isolated facial weakness or sensory symptoms in face or limbs alone may occur.
- Reduced common carotid or superficial temporal pulsation, and bruit over carotid artery in the neck or over orbit maybe heard.
- Occasionally, cholesterol crystals maybe seen in the retinal vessels on fundoscopy.

Vertebro Basilar Territory

- Ataxia, dysarthria, hemianopia, diplopia, sudden fall (drop attacks), weakness on both sides or on one side, paraesthesia on both sides, difficulty in swallowing, vertigo and tinnitus may occur. More than one symptom may occur simultaneously and vertigo is a common symptom, but isolated vertigo without other signs or symptoms is rare.

Investigations

Routine tests for TIA	Additional tests
- Full blood count, ESR	***In vertebro basilar TIAs***
- Serological tests for syphilis	- Lying and standing BP
- Blood glucose, urea, proteins	- 24 hours ECG monitoring
- Chest X-ray, ECG	- X-ray of cervical spine
	- MRI angiography
In younger patients	
- Antinuclear factors	***In carotid TIAs***
- Cholesterol	- CT scan or diffusion weighted MRI of head
- Coagulation studies (anticardiolipin antibodies,	- Carotid Doppler study
protein C and S, antithrombin III)	- Arteriography, CT or MR angiography

Diagnosis

- TIAs will have to be differentiated from focal seizures, hypoglycaemia and migraine.
- TIA typically has a rapid onset, and maximal intensity usually is reached within minutes.
- Younger age, previous history of migraine (with or without aura), and associated headache, nausea or photophobia are more suggestive of migraine than TIA. In general, migraine aura tends to have a marching quality for example symptoms such as tingling may progress from the fingers to the forearm to the face. Migraine aura also is more likely to have a more gradual onset and resolution with a longer duration of symptoms than in a typical TIA.
- Work up in a case of TIA should include evaluation for risk factors for stroke. They are the following:
  - Hypertension
  - Diabetes
  - Hyperlipidaemia
  - Arterial disease affecting the heart and limbs
  - Cardiac disease (valvular and ischaemic)
  - Smoking

Risk Assessment for Occurrence of Stroke

- Calculate ABCD2 score; high risk of early stroke if ABCD2 score ≥4 points

- Age >60 years, 1 point
- BP >140/90 mmHg, 1 point
- Clinical features
  - Speech disturbance, 1 point
  - Unilateral weakness, 2 points
- Duration
  - ≥10 minutes, 1 point
  - ≥1 hour, 2 points
- Diabetes, 1 point

Treatment

- Positioning the patient with the head of the bed flat so as to increase blood flow to brain.
- Patients who score 4 and above on ABCD2 are at high risk of recurrent stroke and should be given immediate aspirin and referred to a higher centre within 24 hours of symptom onset for assessment and investigation.
- If the ABCD2 score is < 4, start aspirin and have specialist assessment within 7 days. People with crescendo TIA (two or more TIAs in a week) should be treated as being at high risk of stroke, even though they may have an ABCD2 score of 3 or below.
- Antiplatelet agents—Aspirin in doses ranging from 75 to 300 mg/day reduces the chances of stroke by 25% and death by 30%. If there is gastric intolerance, dose maybe reduced to 75 mg/day or clopidogrel (75 mg) should be given. Combination of aspirin and clopidogrel is not more beneficial than aspirin alone.
- Correction of risk factors—This includes treatment of hypertension, diabetes and hyperlipidaemia, correction of valvular heart diseases and cessation of smoking. However, BP should not be lowered acutely unless, it is above 220 mmHg systolic or 120 mmHg diastolic when it should be lowered gradually.
- Anticoagulants—Role of anticoagulants in TIA has not been properly assessed but these agents are given if aspirin fails or if there is a definite cardiac source of embolism (e.g. atrial fibrillation).
- Surgery—Once a carotid territory TIA is diagnosed, carotid imaging should be performed immediately, and if it shows >70% stenosis, patient should be immediately referred for carotid endarterectomy. Carotid artery stenting is another option in place of carotid endarterectomy. Medical treatment is continued. Totally occluded vessels are not amenable for surgical treatment.

Q. What is stroke in evolution?

- In some patients, focal neurological deficit may worsen stepwise over few hours or days. It is usually due to gradual occlusion of major blood vessel by a thrombus. This picture may also occur in a rapidly growing tumour or subdural haematoma. Management includes adequate initial clinical evaluation, periodic review and CT scan

to rule out alternate cause, followed by anticoagulants. Initially, heparin is used (1000 units/hour) as infusion and rate is adjusted to maintain aPTT at 1½ times the control value. Simultaneously, oral anticoagulants are started (warfarin or dindevan) and dose is adjusted to maintain prothrombin time to 1½ times the control value (when heparin can be withdrawn).

Q. Discuss briefly about Wallenberg's syndrome (lateral medullary syndrome).

- It is always due to an infarct that is located at dorsolateral medulla and occurs due to occlusion of posterior inferior cerebellar artery, its branch or parent vertebral artery itself. Symptoms consist of sudden onset vertigo, vomiting, dysphagia and ataxia. At times syndrome is incomplete and various partial combinations maybe seen.

Signs

Ipsilateral signs	Contralateral signs
- Facial numbness (VII)	- Analgesia over trunk and extremities (spinothalamic)
- Diplopia (VI)	- Hemiparesis (mild, unusual)
- Nystagmus	
- Ataxia (cerebellar)	
- Horner's syndrome	
- Palatal palsy (IXth and Xth nerve lesions)	

Q. How do you differentiate between haemorrhagic, thrombotic and embolic strokes?

Feature	Haemorrhagic	Thrombotic	Embolic
- Time of onset	During activity	In sleep	Any time
- Progression	Over minutes and hours	On waking up or over hours	Within seconds
- TIAs	Absent	Present	Present
- Vomiting	Recurrent	Absent or occasional	Absent or occasional
- Headache	Prominent	Mild or absent	Mild or absent
- Early resolution (within minutes or days)	Unusual	Variable	Possible
- Meningeal irritation	Maybe present	Absent	Absent
- Carotid bruit (and absent pulse)	Not seen	Highly supportive	Possible
- Valvular heart disease and atrial fibrillation	Not seen	Unusual	Highly supportive
- CT scan	Haemorrhage	Pale infarct (normal in early stage)	Pale infarct (normal in early stage), haemorrhagic infarct in some cases

- In a given case, it may not be possible to differentiate with absolute certainty as none of the above-mentioned features are exclusive and there is marked overlap.

Q. Discuss clinical features and management of cerebral infarct.

- Caused by embolism, thrombosis or due to severe hypotension/hypoperfusion of brain.
- Thromboembolism is characterised by sudden or rapid onset of focal neurologic signs. Preceding TIAs may have occurred. Neurologic examination shows signs attributable to a brain region supplied by a single cerebral or posterior circulation artery.

Clinical Features

- In the prehospital phase, Cincinnati Prehospital Stroke Scale is a popular scale to detect stroke early. It can be remembered by acronym "FAST" – *F*acial asymmetry, *A*rm drift (while holding arms in front of body), *S*peech abnormality (dysarthria or aphasia) and *T*ime of onset.
- Various features of ischaemic stroke are related to the artery blocked by embolus or thrombus (see box).

- Left anterior circulation (supplied by left internal carotid artery and its anterior cerebral and middle cerebral branches)—right hemiparesis, hemisensory loss, hemianopia, aphasia
- Right anterior circulation (supplied by right internal carotid artery and its anterior cerebral and middle cerebral branches)—left hemiparesis, hemisensory loss, hemianopia; left neglect, decreased awareness of the deficit, abnormal drawing and copying
- Middle cerebral artery—Global aphasia if dominant hemisphere is involved and contralateral hemispatial neglect if nondominant hemisphere is involved; motor and sensory deficits of the side opposite to the occlusion, involving the face and arm, and to a lesser extent, the leg; deviation of eyes toward the side of occlusion; may have homonymous hemianopia
- Anterior cerebral artery— Contralateral motor and sensory deficits, more prominent in the leg than the arm (face and tongue usually spared); lack of concern and disinhibition; incontinence; primitive frontal lobe reflexes (grasp and suck)
- Vertebro basilar circulation involving brain stem and cerebellum—vertigo, diplopia, crossed motor or sensory signs (one side of the face and the contralateral body), ataxia; bilateral motor or sensory signs
- Left posterior cerebral artery territory—right hemianopia, alexia without agraphia; right hemisensory symptoms
- Right posterior cerebral artery territory—left hemianopia, left hemisensory symptoms, topographic disorientation (inability to orient to surroundings)

Management

- Successful care of acute stroke patients relies on "Stroke Chain of Survival" that has 8 Ds.

Stroke Chain of Survival

- Detection of onset of stroke signs and symptoms
- Dispatch through activation of emergency medical services and prompt response
- Delivery of patient to a pre-notified hospital, with appropriate pre-hospital care
- Door (immediate emergency department triage)
- Data compilation including head CT scan
- Decision regarding potential therapies
- Drug therapy
- Disposition (timely admission to stroke unit or transfer)

- Initial investigations, monitoring and treatment are carried out simultaneously.
- In the emergency department following should be observed so as to maximise the chances of thrombolysis:
  - Emergency physician evaluation within 10 minutes of arrival.
  - Stroke team notification within 15 minutes of arrival.
  - Brain computed tomography within 25 minutes and interpretation within 45 minutes of arrival.
  - If indicated, door-to-drug treatment time of less than 60 minutes from arrival.

Initial Evaluation

- Cardiovascular status:
  - BP
  - Cardiac function and ECG
- Degree of neurological deficit and vascular territory involved.

- Metabolic status:
  - Blood sugar
  - Presence or absence of hypoxia
  - Renal functions
  - Electrolyte status
- Haematological parameters:
  - Haemoglobin
  - Coagulation parameters

Note: Except for blood sugar, other tests maybe done but should not delay initiation of thrombolytic therapy.

Other Investigations

- CT scan—to confirm infarct and to rule out haemorrhage, tumour and subdural haematoma. In case of an infarction, there is a period of 1–2 days before a focal area of hypodensity appears on CT scan. Only large infarcts with oedema can be visualised during the first few hours of stroke. The main role of CT scan, if the patient comes within 3–4½ hours of onset of symptoms, is to exclude an intracranial haemorrhage so as to decide about thrombolytic therapy.
- MRI scan—diffusion weighted imaging is most sensitive and specific for acute ischaemic stroke.
- CT angiography and MR angiography—if either intra-arterial fibrinolysis or mechanical thrombectomy is contemplated for management but should not delay intravenous rtPA if indicated.
- Chest radiography—particularly if patient is unconscious and is at risk of developing aspiration pneumonia.

Monitor (in all Patients)

- Neurological and cardiovascular status frequently in a day.
- Metabolic parameters daily.

Treatment

General

- Maintain adequate airway with periodic clearance of secretion and chest physiotherapy in unconscious patients.
- Administer oxygen if oxygen saturation is below 94%.
- Treat hypoglycaemia with 50% dextrose; treat hyperglycaemia with insulin, if serum glucose >180 mg/dL.
- Continuous cardiac monitoring for ischaemic changes or atrial fibrillation.
- Avoid dextrose infusion unless indicated. Infuse normal saline at 50 mL/hour unless otherwise indicated.
- Avoid hyperthermia.
- Skincare by changing position once in 2 hours to prevent bed sore.
- Nil per orally initially. Nasogastric tube (if unable to swallow) to maintain adequate fluid balance or to prevent vomiting by keeping stomach empty and depending on the need.
- Bladder catheterisation, if incontinence or retention has occurred.
- Passive movements of limbs to prevent contractures, oedema of the limb, venous stasis and pulmonary embolism.

Specific Measures

- BP—many show reactive hypertension. A rapid reduction in BP can increase the size of infarct.
  - Urgent reduction is required only if systolic BP is above 220 mmHg, diastolic pressure is above 120 mmHg or mean arterial pressure is above 130 mmHg.
  - If BP is not elevated to that extent but the patient has pulmonary oedema, renal failure, acute myocardial infarction, etc. antihypertensives are required. Otherwise, BP is gradually reduced over several days.
  - In patients who are candidates for thrombolytic therapy, antihypertensives are recommended if systolic BP >185 mmHg or diastolic >110 mmHg.
  - Drugs most often used include intravenous labetalol, enalapril or sodium nitroprusside.
- Antioedema measures—large infarcts will show significant oedema that maybe reduced by antioedema measures. However, hypovolaemia must be avoided.
  - Mannitol 20% IV over 20 minutes (0.25 g/kg) three to four times a day.
  - Glycerol 30 mL orally three to four times a day.
  - Frusemide 20 mg IV three times a day.

- These agents at best may only be life saving by preventing brain herniation, and do not reduce the severity of morbidity. They are not necessary in smaller infarcts, where they may actually result in unnecessary dehydration and electrolyte imbalance.
- Measures to reduce the size of cerebral infarct by attempts to salvage tissue at ischaemic penumbra.
  - By avoiding reduction in cerebral perfusion through preventing rapid reduction of BP.
  - Maintain normal blood sugar levels (avoid infusion of dextrose if blood sugar is normal).
  - Avoid raised body temperature (using antipyretics and cooling blankets).
  - Avoid hypoxia.
  - Maintain normal haemoglobin levels.
  - Thrombolysis (see below).
  - Intra-arterial devices for clot extraction or clot maceration.

Anticoagulants

- Role of heparin in acute stage is controversial and at present not recommended. Anticoagulants are recommended only when mild cerebral ischaemic event occurs in presence of:
  - Recent myocardial infarction where anticoagulants are recommended for a period of 3 months.
  - Previous myocardial infarction with ventricular akinetic segment or ventricular aneurysm.
  - Presence of other cardiac conditions as noted above.
  - Presence of prosthetic valves.
  - Thrombotic stroke as indicated by progressive stroke (though use of heparin is still controversial in this setting).
- Not recommended for patients with moderate to severe strokes because of an increased risk of serious intracranial haemorrhagic complications.
- Subcutaneous administration of anticoagulants is recommended for treatment of immobilised patients to prevent deep vein thrombosis.

Thrombolytic Therapy

- Intravenous recombinant tissue plasminogen activator (rTPA) has been shown to be beneficial when initiated within the first 3–4½ hours of an ischaemic stroke in a patient above 18 years of age. However, there is a significant risk of intracerebral bleeding in stroke patients treated with thrombolytic agents.
- Contraindications:
  - Blood on CT scan
  - Possible SAH
  - A large hypodense lesion in a distribution consistent with the neurologic examination
  - Active internal bleeding
  - Bleeding diathesis
  - Systolic pressure >185 mmHg and diastolic pressure >110 mmHg
  - Major neurosurgery or head injury within 3 months
  - History of intracranial haemorrhage or AV malformation
- Dose: 0.9 mg/kg (maximum 90 mg) with 10% of total dose as bolus and rest over 1 hour.
- Intra-arterial (through carotid artery) rTPA can be given in selected patients up to 6 hours after onset.

Other

- Intra-arterial thrombectomy using mechanical devices.

Secondary Prophylaxis

- It is similar to the primary prevention discussed below. Antiplatelet agents should be started within 24–48 hours.
- Usefulness of clopidogrel for the treatment of acute ischaemic stroke is not well established.

Mortality

- In 1st week—mortality depends on size of infarct and cardiovascular status (difficult to control).
- In later weeks—mortality depends on infections of lung, urinary bladder, IV sites, or metabolic disturbances like water and electrolyte imbalance (easy to prevent and correct).
- Later management includes rehabilitation, adequate control and maintenance of risk factors. Rehabilitation should involve family members, and includes motor, sensory, cognitive and psychological measures, and attempts at occupational rehabilitation.

Q. Discuss briefly about lacunar infarction.

- Small deep infarcts, usually <15 mm in size secondary to diseases of small perforating branches of brain. May or may not present with symptoms or signs.
- The occlusion maybe due to microatheroma and lipohyalinosis that are associated with hypertension, smoking and diabetes, or to microembolism from the heart or carotid arteries.

Clinical Features

Pure Motor Stroke

- Occurs due to lesion in the posterior limb of internal capsule (which carries descending corticospinal and corticobulbar tracts) or basis pontis.
- Clinical course is often stuttering, with the symptoms developing in a stepwise fashion over several hours.
- Hemiparesis or hemiplegia typically affects face, arm and leg equally; however, the face or leg can be involved to a lesser extent than other regions, and occasionally, only arm or leg weakness is noted.
- Motor aphasia also present, if lesion in genu and anterior limb of internal capsule.
- Occurs due to involvement of lentico-striate artery, a branch of middle cerebral artery.

Ataxic Hemiparesis

- Second most frequent lacunar syndrome.
- Combination of cerebellar and motor symptoms, including weakness and clumsiness, on the ipsilateral side of the body.
- Usually affects the leg more than the arm.
- The most frequent sites of infarction are the posterior limb of the internal capsule, basis pontis and corona radiata.

Pure Sensory Stroke

- Persistent or transient numbness and/or tingling on one side of the body.
- Occasionally, pain, burning or other unpleasant sensations.
- The most frequent site is thalamus.

Mixed Sensorimotor Stroke

- Hemiparesis or hemiplegia with ipsilateral sensory impairment.
- The infarct is usually in the thalamus and adjacent posterior internal capsule.

Dysarthria-clumsy Hand Syndrome

- Combination of facial weakness, severe dysarthria, and dysphagia with mild hand weakness and clumsiness.

Q. Discuss the clinical manifestations and treatment of primary subarachnoid haemorrhage (SAH).

- Subarachnoid haemorrhage (SAH) accounts for about 10% of strokes. In more than 80% of cases, it is due to rupture of aneurysms located at circle of Willis or its main branches. Other causes are:
  - Arteriovenous malformations
  - Extension from intracerebral bleed
  - Trauma
  - Mycotic aneurysms
  - Anticoagulant therapy
  - Bleeding diathesis
- SAH causes profound reductions in CBF, reduced cerebral autoregulation and acute cerebral ischaemia.

Risk Factors

- Important risk factors include alcohol consumption, smoking and hypertension. Use of sympathomimetic drugs, including cocaine and phenylpropanolamine is also a risk factor.
- Certain genetic syndromes have also been associated with an increased risk of SAH. These include autosomal dominant polycystic kidney disease and type IV Ehlers–Danlos syndrome.

Clinical Features

- The characteristic is abrupt severe headache with or without associated vomiting. Onset maybe associated with any activity that results in rise in BP. Consciousness maybe lost and a seizure may occur.
- A few patients may have milder warning headaches (sentinel headaches) in 2–8 weeks preceding the major haemorrhage.

- Onset of headache maybe associated with additional signs and symptoms including nausea, vomiting, stiff neck, a brief loss of consciousness or focal neurological deficits (including cranial nerve palsies).
- Seizures may occur in up to 20% of patients after SAH, most commonly in the first 24 hours and more commonly in SAH associated with intracerebral haemorrhage, hypertension, and middle cerebral and anterior communicating artery aneurysms.
- Examination reveals variable degree of consciousness with signs of meningeal irritation. Focal neurological deficits at onset suggest bleeding into adjacent brain parenchyma. Subhyaloid haemorrhage on fundoscopy is seen occasionally.
- In posterior, communicating artery aneurysm and IIIrd cranial nerve palsy is observed.

Investigations

CT Scan

- The scan shows blood in the subarachnoid space (if done in the first few days) and presence of intracerebral haematoma, hydrocephalus, associated brain ischaemia and occasionally location of aneurysm itself.

Lumbar Puncture

- It should be done if clinical suspicion is high but CT scan fails to show subarachnoid blood, and there is no mass effect. CSF will be uniformly blood stained in the initial hours and becomes xanthochromic in later days (first appears after 4–6 hours of the bleed).

Angiography

- It is needed to locate the site of aneurysm which has bled, and other details that neurosurgeon needs to know in order to ligate the aneurysm adequately.
- It should be performed in all patients fit for surgery (age <65 years, not in coma).

MR Angiography (MRA)

- It can demonstrate aneurysms >5 mm in size with great accuracy. However, due to lack of easy availability and time required for performing it, MRA has not replaced conventional angiography.

CT Angiography

- A rapid, readily available, less invasive alternative to catheter angiography and is equivalent to conventional angiography for demonstrating larger aneurysms.
- Maybe considered when conventional angiography cannot be performed in a timely fashion.

Management

- Immediately shift the patient to a centre where neurosurgical care is possible unless patient is too ill to be shifted. Re-bleed is usual in the first 2 weeks, which is often fatal. There is at least a 3–4% risk of re-bleeding in the first 24 hours and then a 1–2% per day risk in the first month. A longer interval from haemorrhage to admission and treatment, higher initial BP, and worse neurological status on admission have been related to recurrent haemorrhage in the first 2 weeks after SAH.
- In properly chosen patient with proper timing of surgery, clipping of aneurysm is followed with very good results. Endovascular coiling to ablate aneurysm is also used in centres with experience.
- Medical treatment of patients with aneurysmal SAH is directed toward the prevention and management of neurological complications (e.g. aneurysm re-bleeding, hydrocephalus, cerebral vasospasm and ischaemia, and seizures) and systemic complications (e.g. hyponatraemia, cardiac arrhythmia and myocardial damage and neurogenic pulmonary oedema).
- Immediate administration of antifibrinolytic agent tranexamic acid (1 g IV, followed by 1 g every 6 hours) maybe useful to reduce the rate of early aneurysm re-bleeding. In some cases, it may worsen cerebral ischaemia.
- Pain management, sedation and control of hypertension are also important in the prevention of aneurysm re-bleeding.
- In conscious patients without evidence of raised ICP, active hypertension treatment is indicated. A target mean arterial pressure of 130 mmHg is recommended, if it is elevated beyond this value. Agents used include labetalol, esmolol or nicardipine. Sodium nitroprusside should be avoided as it may elevate ICP.
- Strict avoidance of hypovolaemia, hypotension, hyperthermia, hyperglycaemia and hyponatraemia are important in preventing delayed cerebral ischaemia.
- Calcium blocking agent nimodipine (60 mg orally every 4 hours) provides a modest but significant improvement in outcome by reducing cerebral arterial vasospasm.
- Anticonvulsants are recommended for prophylaxis.
- Absolute bed rest for 4 weeks is advised followed by gradual resumption of physical activities.

Q. Briefly outline the risk factors, clinical features, diagnosis and management of intracerebral haemorrhage.

- Occurs secondary to hypertension where penetrating branches undergo degeneration and develop microaneurysms within the brain. Common sites of bleeding in order of frequency are:
  - Putamen
  - Thalamus
  - Frontal or parietal lobes
  - Pons
  - Cerebellum

Risk Factors

- Incidence of ICH increases exponentially with age and is higher in males than in females.
- Most spontaneous haematomas are attributed to chronic arterial hypertension.
- Other risk factors are ageing (which produces cerebral amyloid angiopathy), alcohol consumption, anticoagulant treatment and antiplatelet therapy.
- Other conditions that may complicate with haemorrhage include brain tumours, dural venous sinus thrombosis, vascular malformations, etc.
- Use of amphetamines or cocaine, cigarette smoking and diabetes mellitus are also associated with increased risk.
- Coagulation disorders and bleeding tendency (e.g. thrombocytopenia) are rare causes of ICH.

Clinical Features

- Clinical features are often indistinguishable from ischaemic stroke, and a CT scan is often required.
- Patients present with a smooth onset of focal neurological deficit over minutes to hours often accompanied by headache and vomiting due to increased ICP.
- More than 90% of patients present with acute hypertension, hyperventilation, tachycardia or bradycardia, central fever and hyperglycaemia. Clinical deterioration occurs in 30–50% of patients, usually within the first 24 hours, and maybe attributable to any combination of haematoma expansion, perihaematoma oedema, hydrocephalus and seizures.
- Involvement of putamen often presents with hemiparesis along with some depression of consciousness.
- Thalamic haemorrhage commonly produces hemianaesthesia more prominently than hemiparesis along with impaired upward gaze.
- A significant haemorrhage into pons is usually a catastrophe as it leads to coma, pinpoint pupils, quadriparesis and a dysconjugate ocular mobility disorder.
- Lobar haemorrhage, depending upon the size and location, produces unilateral hemiparesis and hemisensory deficits along with speech impairment.
- Cerebellar haemorrhage presents with sudden onset of headache, vertigo, vomiting, ataxia and sometimes paralysis of conjugate gaze to one side. Initially, no change in the level of consciousness occurs; however, a mass effect produces brainstem compression later and leads to coma.

Consequences

- Expansion of haematoma that occurs over several hours.
- Hydrocephalus.
- Cerebral oedema (may produce delayed worsening).

Diagnosis

- CT scan or MRI brain.
- Cerebral angiography in young patients with no obvious risk factors for intercerebral haemorrhage.

Management

- Management is on similar lines as in infarcts.
- Patients with Glasgow Coma Scale < 8 often require intubation and ventilation.
- Control of raised ICP.
- Administer phenytoin if seizures develop.

- BP should be reduced cautiously:
  - In previously hypertensive patients if systolic pressure >180 mmHg or diastolic pressure >105 mmHg, it should be reduced to 160/100 mmHg (but not more than 20 mmHg reduction from baseline).
  - In previously normotensive patients if BP is above 160/95, it should be reduced to 150/90 mmHg.
- Certain intracerebral haematomas are amenable for surgical evacuation, e.g. patients with cerebellar haematoma who are deteriorating neurologically or who have brain stem compression and/or hydrocephalus should undergo surgical evacuation of haematoma. Patients with lobar haematoma who are gradually worsening neurologically may also be considered for evacuation.
- If the patient presents within 3 hours of onset, recombinant activated factor VII (rFVIIa) maybe administered as it has been shown to reduce haematoma expansion. However, its role is controversial. Potential adverse effects include increased incidence of arterial thromboembolism.

Q. How will you prevent occurrence of first episode of stroke?

Q. Discuss in brief the primary prevention of stroke.

- Stopping smoking
- Control of diabetes
- Lowering systolic BP by 10 mmHg is associated with a reduction in the risk of stroke by about one-third, irrespective of baseline blood pressure levels. Long-acting dihydropyridine calcium channel blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers are possibly more effective than other classes of antihypertensive drugs.
- Antiplatelet agents and anticoagulants in patients with atrial fibrillation.
- Reducing LDL cholesterol to 100 mg/dL using statins.
- Prophylactic aspirin in males above 50 years and females above 65 years (controversial).
- Avoiding routine use of hormonal replacement therapy, as its use is associated with increased risk of stroke.
- For asymptomatic patients who are detected to have carotid artery stenosis of 60–99%, carotid endarterectomy maybe considered.
- Aspirin and/or anticoagulants in patients with atrial fibrillation and high risk of embolism.

Q. Give a brief account of cerebral venous thrombosis.

- Cerebral venous thrombosis is the cause of approximately 1–2% of strokes in young adults.
- Superior sagittal sinus is most commonly involved. Thrombus may extend into transverse and sigmoid sinuses.
- Deep venous system thrombosis (e.g. thrombosis of internal cerebral veins and vein of Galen or straight sinus) is less common.

Causes

Local causes
- Trauma to the dural sinuses
- Infection in structures adjacent to the dural sinuses
- Otitis media
- Mastoiditis
- Sinusitis
- Tonsillitis
- Invasion or compression of venous sinuses by neoplastic processes

Systemic causes
- Hypercoaguable states
  - Oral contraceptive use
  - Pregnancy
  - Malignancy
  - Protein C or protein S deficiency
  - Presence of lupus anticoagulant
- Dehydration

Pathophysiology

- Cerebral venous thrombosis results in elevated cerebral venous pressure that produces decline in arterial perfusion pressure.
- If reduction of arterial perfusion pressure is severe enough and prolonged enough, venous infarction occurs and haemorrhage may ensue.

Clinical Features

- Unlike arterial thrombosis, symptoms tend to develop slowly or subacutely.
- Most patients develop generalised neurologic symptoms with headache as a common first clinical symptom.
- Nausea and vomiting are common.
- Papilloedema due to elevated ICP.
- Some patients develop seizures, or focal sensory or motor deficits.
- Cranial nerve palsies may occur, particularly when there is involvement of petrous sinuses.
- In some cases, coma or death.
- Classical picture of superior sagittal sinus thrombosis is bilateral or alternating deficits and/or seizures. Cavernous sinus thrombosis presents with chemosis, proptosis and painful ophthalmoplegia.

Diagnosis

- CT or MR venography
- CT or MRI to detect secondary parenchymal lesions
- CSF examination in appropriate clinical context to rule out meningitis or SAH
- Coagulation studies in appropriate patients

Treatment

- Supportive measures such as hydration, appropriate antimicrobials, control of seizures with anticonvulsants and control of ICP.
- Intravenous heparin to halt progression of thrombosis. Can be given even if haemorrhage is present.
- Intradural thrombolysis in patients whose clinical status worsens while on anticoagulation.
- Mechanical thrombectomy.

Q. Describe the pathogenesis, clinical features and management of Alzheimer's disease.

- Alzheimer's disease is a progressive neurodegenerative disease resulting in decline in cognitive functions together with declining activities of daily living (ADL) and behavioural disturbances.
- It is the most common cause of cognitive impairment in elderly persons. From the age of 60 onwards up to 80 years, incidence and prevalence of AD increases exponentially with age, doubling every 5 years.

Pathology

- The pathological process consists principally of neuronal loss, principally in the temporoparietal cortex but also in the frontal cortex, together with an inflammatory response to the deposition of senile plaques and neurofibrillary tangles.
- Senile plaques and neurofibrillary tangles are regarded as hallmark of Alzheimer's disease, though they may also be present with normal aging.
- Senile plaques consist of extracellular deposition of congophilic, insoluble material that is amyloid-β (Aβ). It is derived from the enzymatic cleavage of a larger membrane protein, the amyloid precursor protein (APP).
- Neurofibrillary tangles represent intracellular paired helical filaments of hyperphosphorylated protein known as tau protein. Tau protein is expressed in neurons and normally acts to stabilise microtubules in the cells.
- Other pathologic features include synaptic degeneration, accumulation of abnormal lysosomes and mitochondria, neuronal loss and glia-mediated inflammation.

Aetiology

- The exact aetiopathogenesis is not known.
- Three hypotheses include cholinergic hypothesis (reduced acetylcholine), amyloid hypothesis and tau hypothesis.

- Genes that increase the probability of sporadic Alzheimer's disease include the allele ε4 of apolipoprotein E (APOE) and the sortilin-related receptor 1. (SORL1) gene (which is involved in cholesterol transport, β-amyloid formation and APP processing).
- Early onset of Alzheimer's disease (onset < 60 years) is uncommon and is usually autosomal dominant. Three gene mutations have been identified: APP gene located on the chromosome 21; the presenilin-1 (PS1) and presenilin-2 (PS2) genes located on chromosomes 14 and 1 respectively.
- Moderate consumption of red wine, increased dietary intake of fruits and vegetables, and the use of nonsteroidal anti-inflammatory drugs are associated with a lower risk.
- Potential acquired risk factors for Alzheimer's disease are shown below.

- Ageing
- Family history of Alzheimer's disease
- Reduced reserve capacity of brain
  - Low educational and occupational attainment
  - Low mental ability in early life
  - Reduced mental and physical activity during late life
- Diet
  - Reduced consumption of fish
  - Increased consumption of dietary fat
- Head injury
- Risk factors associated with vascular disease
  - Hypercholesterolaemia
  - Hypertension
  - Smoking
  - Obesity
  - Diabetes

Clinical Features

- It is an insidiousonset disease with symptoms in 3 domains: cognitive, behavioural and functional. Mild cognitive impairment is characterised as a transitional stage between normal ageing and Alzheimer's disease.
- The patient has disturbances of memory, language and visual skills:
  - There is an impaired ability to learn new things and recall previously learnt information. An inability to retain recently acquired information is typically the initial symptom, whereas memory for remote events is relatively spared until late. Episodic memory impairment (memory for personally experienced events in a particular temporal and spatial context) is an important cognitive deficit. This can be tested by the three words recall item and the orientation items of the mini-mental state examination (MMSE).
  - Impairment of semantic memory (knowledge of public events, words and of the associations between concepts), working memory (ability to manipulate short-term memory representations) and executive functions (coordination of multiple cognitive processes) are often present.
  - A decline in language function and increased difficulty with names and understanding what is being said (nominal and comprehensive dysphasia). The first manifestations of language dysfunction usually include word finding difficulties, circumlocution, and reduced vocabulary in spontaneous speech and anomia.
  - An impaired ability to carry out motor activities despite intact motor function (dyspraxia).
  - Failure to recognise or identify objects despite intact sensory function (agnosia).
- There is a gradual decline in ADL that ultimately leads to profound disability and dependence on others.
- Other features include behavioural problems, psychotic symptoms and depression. Psychotic symptoms are not the presenting features but develop later during the course of disease. Occurrence of psychosis during the initial stages of dementia suggests other diagnoses such as dementia with Lewy bodies. Persecutory delusions occur in nearly 50% of the patients.
- It is important to differentiate between Alzheimer's disease and other treatable causes of dementia (see "dementia").
- Pneumonia is a common cause of death because aspiration is common due to impaired swallowing mechanisms in the later stages. Other common causes of death include complications from urinary tract infections and falls.

Laboratory Investigations

- These are carried out to exclude a treatable cause of dementia (see "dementia").
- Common investigations are blood chemistry, a complete blood count, tests for syphilis, serum levels of vitamin B_{12} and thyroid functions.
- A CT head is usually done to exclude an intracranial pathology. An MRI may show atrophy in the hippocampus, mesial and lateral temporal, isthmus cingulate and orbitofrontal areas. It can help exclude normal pressure hydrocephalus. Focal frontal or anterior temporal atrophy suggests a diagnosis of frontotemporal dementia. Large white matter abnormalities indicate a vascular dementia, particularly if the history is one of a stepwise decline in cognitive function.
- High resolution functional MRI may distinguish AD from normal aging.
- Cerebrospinal fluid is normal but may show slight elevation in protein content. There is an increase in total tau and phosphorylated tau but a decrease in amyloid-beta ($A\beta$).
- Functional neuroimaging studies such as PET and SPECT scans can provide a supporting role in diagnosis. PET shows decreased FDG uptake in hippocampus, parietotemporal cortex and posterior cingulate cortex.

Diagnosis

- Criteria for a diagnosis of clinically probable Alzheimer's disease are the presence of an episodic memory deficit in combination with impairment of at least one other cognitive domain. Frequently affected domains at an early stage are executive functions and word finding. There must be a significant impact on ADL and no alternative explanations (delirium, medication, comorbidity and depression).
- MMSE is useful in the initial evaluation of patients with suspected dementia.
- Cognitive aging (age-related cognitive decline) refers to age-related decline that selectively affects specific cognitive processes, including delayed recall, processing speed and executive functions. Familiarity of past objects and persons is usually not affected in age-related cognition decline.

Management

Cognitive Deficits

- Cholinesterase inhibitors provide modest improvement in symptoms and reduction in the rate of cognitive decline. They inhibit acetylcholinesterase, the enzyme that degrades acetylcholine in the synaptic cleft, thereby increasing the availability of acetylcholine. These drugs include donepezil, rivastigmine and galantamine. Common side effects include nausea, vomiting, diarrhoea and weight loss.
  - Donepezil is started at a dosage of 5 mg daily at bedtime and increased to 10 mg daily after 1–4 weeks.
  - Galantamine is started at a dosage of 4 mg twice daily and gradually titrated to 12 mg twice daily with step-ups at 1–4 week intervals.
  - Rivastigmine is started at a dosage of 1.5 mg twice daily and titrated over 1–3 months to 6 mg twice daily.
- In moderate to severe cases, memantine, an N-methyl-D-aspartate (NMDA) antagonist maybe added to cholinesterase inhibitors. It is believed to protect neurons from glutamate-mediated excitotoxicity.
- Other agents include vitamin E, statins and NSAIDs, though their exact role is not clear.

Co-Morbid Conditions

- Optimal management should be provided for any co-morbid conditions including visual or hearing deficits, dental problems and other common medical illnesses.

Behavioural Problems

- Treatment of associated behavioural problems by non-pharmacologic and pharmacologic interventions (psychotropic agents) should be prescribed. Atypical antipsychotic drugs (risperidone and olanzapine) are preferred for the management of psychosis. For depression serotonin reuptake inhibitors (e.g. citalopram, escitalopram and sertraline) are used.

Education

- Education of caregiver is very important in patients with Alzheimer's disease.

Q. Describe the aetiology, clinical features and diagnosis of Parkinson's disease.

Q. What is parkinsonism? How would you classify parkinsonism? Discuss the management of idiopathic parkinsonism.

Parkinsonism

- Parkinsonism is a clinical syndrome involving bradykinesia, plus at least one of the following three features: tremor, rigidity and postural instability. All patients with Parkinson's disease have parkinsonism, but not all patients with parkinsonism have Parkinson's disease.

Classification

Primary parkinsonism
- Paralysis agitans or Parkinson's disease or idiopathic parkinsonism

Secondary (symptomatic)
- Post-encephalitic (post-encephalitis lethargica)
- Toxins—e.g. MPTP (methyl-phenyl-tetrahydropyridine), manganese, carbon monoxide
- Drugs—e.g. reserpine, phenothiazines, butyrophenones (including haloperidol), α-methyldopa, metoclopramide
- Ischaemic (vascular parkinsonism)
- Tumours in basal ganglion
- Punch-drunk syndrome in boxers
- Infections—e.g. HIV, influenza

Parkinsonism plus (degenerative disorders with prominent additional neurological features)
- Progressive supranuclear palsy, multiple system atrophy (MSA) (striatonigral degeneration, Shy-Drager syndrome, sporadic olivopontocerebellar atrophy), diffuse Lewy body disease, Wilson's disease, Huntington's disease (HD) in children

- Paralysis agitans (primary parkinsonism) is a degenerative disorder.
- Parkinsonism plus are group of degenerative disorders that have additional neurological signs other than that of parkinsonism. For example multiple system atrophy (MSA) includes variable combination of parkinsonism (poor response to L-dopa), cerebellar, pyramidal and autonomic degeneration. MSA encompasses three syndromes: a predominance of parkinsonian features (MSA-P subtype), Shy–Drager syndrome and predominance of cerebellar ataxia (MSA-C subtype). Autonomic dysfunction results in urinary symptoms (urge incontinence and incomplete bladder emptying), erectile dysfunctions in males, orthostatic hypotension and chronic constipation.
- Secondary (symptomatic) parkinsonism includes a group of disorders where aetiological agents are identifiable.

Pathology of Parkinson's Disease (Paralysis Agitans)

- There is loss of pigmented cells and deposition of Lewy bodies in locus coeruleus, followed by substantia nigra. This results in degeneration of nigro striatal pathway. These cells normally synthesise dopamine. With degeneration of these cells, dopamine level in the striatum gets depleted; this is the major chemical pathology in Parkinson's disease. Degeneration of non dopaminergic neurons also occurs, but it usually occurs later in the course of the disease. The loss of non dopaminergic neurons contributes to the non-motor features.

Clinical Features

- Two environmental factors are recognised to lower the risk for Parkinson's disease—cigarette smoking and coffee drinking.
- Affects both sexes equally and starts usually during sixth decade and later. Occasionally, it may appear during fifth decade. Initial symptoms maybe easy tiredness or muscular aches, usually unilaterally. Mild slowness of activity or depression maybe present. Later, classical combination of tremor, rigidity and hypokinesia appear.

Tremors

- It is classically a tremor at rest and is compound (called pill-rolling tremor) occurring at wrist and fingers on one side first that decreases with action. At times, action or postural tremor may also be present. Tremor may also occur at head, jaw or lower limbs.

Rigidity

- Hypertonia is due to rigidity. When tremor is present, it adds cog wheeling character to the basic lead pipe hypertonia (cogwheel rigidity). It is unilateral in the beginning of disease.

Hypokinesia/Akinesia

- It is difficulty in initiating the motor acts. This results in delay or slowness of motor act after intention to start.

Bradykinesia

- It is the paucity or slowness of movements. Some physicians consider hypokinesia under the term bradykinesia when it is defined as slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions. There is reduced movement in acts like getting up, adjusting posture, walking, etc. Two common features are reduced arm swing on one side (which is often misinterpreted by patients and physicians as an orthopaedic problem) and repetitive supination/pronation of hands. Face looks blank and expressionless ("masklike face"). Amplitude of writing declines near the end of a sentence.

Disturbed Postural Reflexes

- Occurs about 5 years after the onset of disease.
- Results in stooped or bent posture with tendency to fall easily, and difficulty in maintaining equilibrium while sitting or standing.
- Muscle strength and tendon jerks remain normal. Glabellar tap becomes positive. Primitive reflexes get released.
- Speech is of low volume and is monotonous. Micrographia is present with a tendency to tail off at the end of a line. Stance is stooped, gait becomes shuffling (festinant), associated arm swinging is absent, and turning about becomes slow and labourious.
- With advancing disease patient assumes fixed flexed postures, remains curled in bed unable to move. Death occurs due to infection (bronchopneumonia and septicaemia).

Others (Non-Motor Features)

- Autonomic dysfunction
  - Orthostatic hypotension
  - Urinary incontinence
  - Impotence
  - Constipation
  - Sialorrhea
  - Anhidrosis
- Neuropsychiatric symptoms
  - Depression
  - Psychosis
  - Dementia
  - Anxiety
  - Panic attacks
- Sensory problems
  - Reduced smell
  - Pain
  - Sleep disorders
  - Restless legs
  - Insomnia
  - Daytime somnolence

Exclusion Criteria for Parkinson's Disease

- Repeated strokes with stepwise progression
- Repeated head injury

- Antipsychotic or dopamine-depleting drugs
- Definite encephalitis and/or oculogyric crises
- More than one affected relative
- Strictly unilateral features after 3 years
- Other neurological features: Supranuclear gaze palsy, cerebellar signs, early severe autonomic involvement, Babinski's sign, early severe dementia with disturbances of language, memory or praxis
- Exposure to known neurotoxin
- Presence of cerebral tumour or communicating hydrocephalus on neuroimaging

Parkinson's Disease Versus Parkinsonism Plus Syndromes

Feature	Parkinson's disease	Parkinsonism plus syndrome
• Pattern of onset	Asymmetrical	Usually symmetrical
• Rigidity	More in peripheral parts	More in axial parts
• Tremors	Resting	Absent or atypical
• Associated features (e.g. dysautonomia, early dementia, cerebellar signs, pyramidal signs, etc.)	Usually absent	Some of them are often present
• Response to L-dopa	Good to excellent	Mild to moderate response initially only
• Progress	Slow	Relatively rapid

Diagnosis

- It is purely clinical and there is no definitive diagnostic test to confirm Parkinson's disease. The four cardinal features of Parkinson's disease can be grouped under the acronym TRAP: *T*remor at rest, *R*igidity, *A*kinesia (or bradykinesia) and *P*ostural instability.
- If clinical features are not strictly within the syndrome or if the disease occurs in earlier life, Wilson's disease will have to be ruled out by estimating serum copper, ceruloplasmin and urinary copper levels.
- Symptoms that suggest a diagnosis other than Parkinson's disease include lack of response to levodopa, hallucinations, prominent and early dementia, early postural instability, severe and early autonomic dysfunction, upward gaze paralysis and involuntary movements other than tremors.
- CT scan or MRI is required if these additional signs are present.
- In atypical cases, PET and SPECT.

Management

- If any offending drug was used, it should be withdrawn. Patient should be seen by a physiotherapist and occupational therapist to help him live well with the disability by modifying home surroundings intelligently.

Drug Therapy

Anticholinergics

- Trihexyphenidyl, benzhexol and orphenadrine are useful in controlling tremors but do not help in other disturbances. They can cause urinary retention, worsen glaucoma and cause confusion in elderly. Hence, they are rarely used as first-line drugs unless patient has severe tremors. They should be avoided if the patient is above 65 years.

Amantadine

- Potentiates endogenous dopamine (pre-synaptic agonist) and has mild antiparkinsonian effect. It is useful early in the disease or in conjunction with L-dopa replacement.
- Important adverse effects include psychosis, oedema and livedo reticularis in the lower limbs.

L-dopa

- Highly effective in treating motor symptoms of bradykinesia and hypokinesia.
- Orally administered L-dopa after absorption crosses blood–brain barrier and gets metabolised to dopamine within the brain. But large amount gets metabolised peripherally to dopamine by decarboxylation. Dopamine cannot cross the blood–brain barrier. By combining a peripheral decarboxylase inhibitor (e.g. carbidopa, and benserazide) with L-dopa, this can be overcome.
- The currently used combinations are given below:
  - L-dopa + carbidopa (4:1 or 10:1 ratio).
  - L-dopa + benserazide (4:1 ratio).
- Drug is started at a low dose (50 mg/dose). Requirement is titrated for frequency per day and strength per dose, slowly. Increments are made once in 2 weeks. Full therapeutic effect may take 4–8 weeks. Maximum dose is 800–1000 mg of L-dopa/day (with peripheral decarboxylase inhibitor). At higher doses, dose-related side effects like dyskinesias and hallucinations occur frequently.
- Over a period of time (after 3–5 years) with progression of disease, control becomes poor and fluctuations in symptoms occur frequently. These fluctuations include wearing-off effect (transient deterioration shortly before the next dose is due), peak-dose dyskinesias (appearance of choreic movements of the trunk, arms and neck during the period of maximum therapeutic efficacy of dopaminergic drugs), and the "on--off" phenomenon (abrupt and transient deterioration occurring frequently without an obvious relation to the dosage schedule). COMT inhibitors (see below) are useful to reduce these response fluctuations. For dyskinesias, amantadine, dopamine receptor agonists and COMT inhibitors are useful.

Dopamine Receptor Agonists

- Post-synaptic dopamine agonists maybe classified as ergot-derived (bromocriptine, pergolide and cabergoline) or non-ergot-derived (apomorphine, pramipexole, ropinirole and rotigotine).
- Ergot-derived dopamine agonists should not be used as first-line treatment for Parkinson's disease as they may produce moderate to severe cardiac valvulopathy and serosal fibrosis (pleural, pericardial and retroperitoneal).
- Non-ergot dopamine agonists are preferable to ergot dopamine agonists and are used as an alternative or an addition to levodopa therapy.
- All types of dopamine agonists can produce impulse control disorders (including pathological gambling, binge eating and hypersexuality) and daytime somnolence.

MAO-B Inhibitors

- Selegiline and rasagiline are MAO-B inhibitors, and have dual role to play.
  - They reduce the metabolism of dopamine and thereby reduce the dose and frequency of administration of L-dopa at all stages.
  - Recent evidences show that they can slow down the degeneration in substantia nigra and are recommended to be used in all patients from early stages of the disease (selegiline 5 mg BD; rasagiline 1 mg OD). However, they can produce serious side effects and drug interactions.

Catechol-O-Methyltransferase (COMT) Inhibitors

- This category of drugs includes tolcapone and entacapone that enhance the benefits of levodopa therapy by reducing the conversion of levodopa to 3-O-methyldopa (which normally competes with levodopa for an active carrier mechanism). This increases the availability of levodopa in the brain. These agents are useful in patients with response fluctuation to levodopa.

Rivastigmine

- Maybe considered in patients with significant dementia.

Summary of Medical Treatment

The figure given below indicates sites of action of various drugs used in Parkinson's disease.

BRAIN

Dopamine receptors (striatum)
Pramipexole
Ropinirole
Bromocriptine
Pergolide

Dopamine ← Levodopa → 3-O-methyldopa
Tolcapone / COMT
DDC (SN)
MAOB — Selegiline

Cholinergic interneurons (striatum)
Trihexyphenidyl
Benztropine

Free radicals

BODY

LNAA transporter

Levodopa → Methylated levodopa
Tolcapone / COMT

DDC Carbidopa

Dopamine
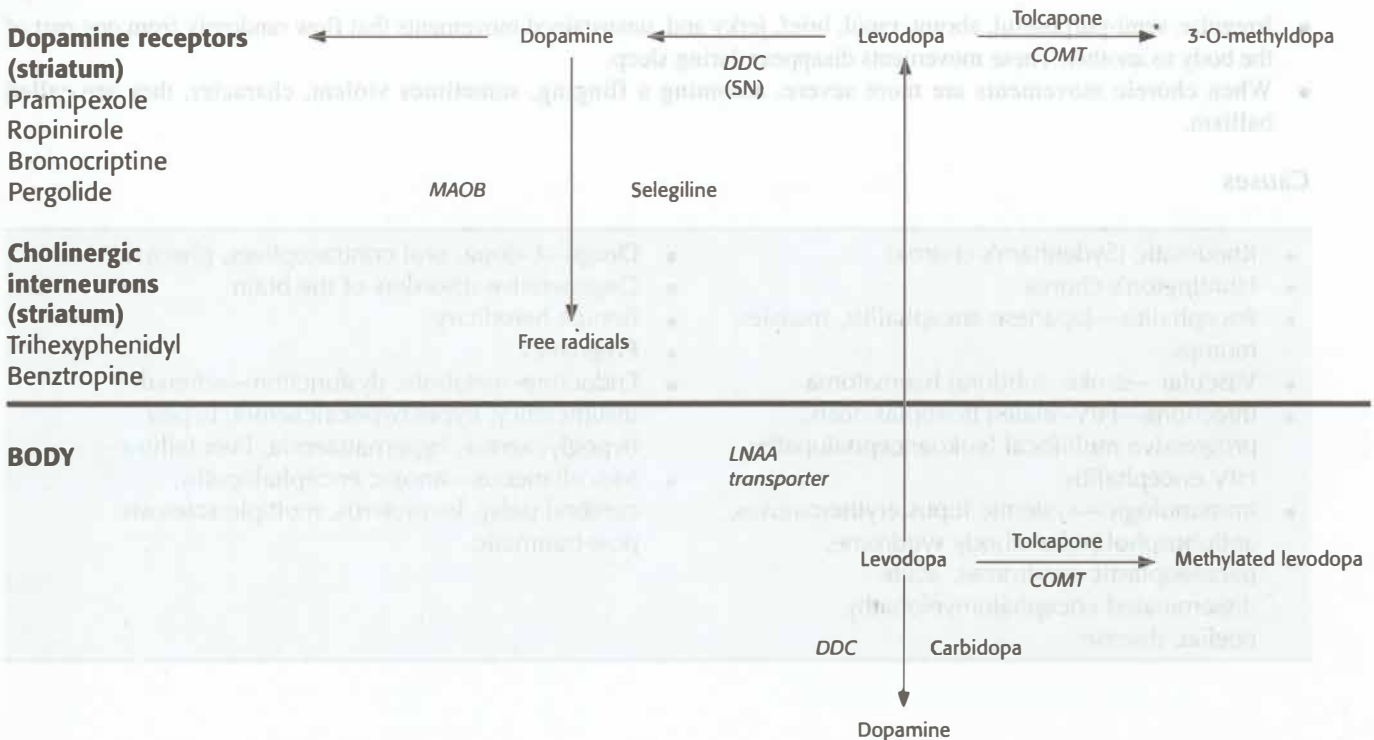
(DDC = Dihydroxyphenylalanine decarboxylase. SN = Substantia nigra. COMT = Catechol-O-methyl transferase. MAOB = Monoamine oxidase B. LNAA = large neutral amino acid)

Surgery

- Stereotactic thalamotomy (ventrolateral nucleus of thalamus) used to be performed in the past is largely given up due to excellent response to drugs.
- Deep brain stimulation (subthalamic nucleus and globus pallidus interna) has been used with success in severe disease.

Q. Discuss briefly the CNS disorders characterised by involuntary movements.

- A movement disorder indicates abnormal movement or paucity of movement either voluntary or automatic which is not attributable to weakness or spasticity or any other medical causes directly interfering with musculoskeletal system. It can be hyperkinetic or hypokinetic.

Hyperkinetic movement disorders	Site of lesion
• Parkinsonism (resting tremors)	Substantia nigra and corpus striatum
• Chorea	Caudate nucleus
• Athetosis	Putamen
• Hemiballismus	Subthalamic nucleus
• Dystonia	Not known
• Myoclonus	Several areas
• Tic	—
• Tremors	—

Chorea

- Irregular, semi-purposeful, abrupt, rapid, brief, jerky and, unsustained movements that flow randomly from one part of the body to another. These movements disappear during sleep.
- When choreic movements are more severe, assuming a flinging, sometimes violent, character, they are called ballism.

Causes

• Rheumatic (Sydenham's chorea)	• Drugs—L-dopa, oral contraceptives, phenytoin
• Huntington's chorea	• Degenerative disorders of the brain
• Encephalitis—Japanese encephalitis, measles, mumps	• Benign hereditary
	• Pregnancy
• Vascular—stroke, subdural haematoma	• Endocrine–metabolic dysfunction—adrenal insufficiency, hyper/hypocalcaemia, hyper/hypoglycaemia, hypernatraemia, liver failure
• Infections—HIV-related (toxoplasmosis, progressive multifocal leukoencephalopathy, HIV encephalitis)	
• Immunologic—systemic lupus erythematosus, antiphospholipid antibody syndrome, paraneoplastic syndromes, acute disseminated encephalomyelopathy, coeliac disease	• Miscellaneous—anoxic encephalopathy, cerebral palsy, kernicterus, multiple sclerosis, post-traumatic

Signs in Chorea

- Involuntary protrusion and retraction of the tongue.
- Respiratory irregularity.
- Inability to hold the hands above head with palms facing each other as it results in pronation of arms so that palms face outwards (pronator sign).
- Milking action of patient's fingers if asked to grasp the physician's fingers (milkmaid sign).

Sydenham's Chorea (Saint Vitus Dance)

- It is the most common cause of chorea in children. It is a self-limiting, non-suppurative complication of group A β-haemolytic streptococcal pharyngitis and it follows acute rheumatic fever by 4–6 months. Severity varies and disorder may continue for a few months.
- Based on the assumption of molecular mimicry between streptococcal and central nervous system antigens, it has been proposed that the bacterial infection in genetically predisposed subjects leads to formation of cross-reactive antibodies that disrupt the basal ganglia function. Inflammation has been seen in caudate nucleus.
- It is a neuropsychiatric disorder; the clinical features include both neurological abnormalities (chorea, weakness and hypotonia) and psychiatric disorders (such as emotional lability, hyperactivity, distractibility, obsessions and compulsions). These abnormalities lead to inability to perform normal activities of daily living including eating, talking, dressing, writing, walking, learning and socialising, and thus impact negatively on the child's quality of life.
- One common sign is motor impersistence, which can be demonstrated by an inability to sustain eye closure or tongue protrusion.
- Evaluation for valvular heart disease is a must. Antistreptolysin-O (ASLO) titres and ESR are often normal.

Treatment

- Symptomatic:
  - Sodium valproate 200–600 mg TID is the first-line drug.
  - If valproate is not effective, risperidone, a potent dopamine D2 receptor blocker, may be given to control chorea. The dose is 1 mg BID that can be increased to 2 mg BID.
  - Haloperidol 0.5–1.5 mg BD or TID is used occasionally.
  - Other drugs include pimozide, carbamazepine, clonidine and phenobarbital.
- Penicillin prophylaxis is necessary to reduce risk of cardiac involvement due to future streptococcal infections.

Huntington's Chorea

- Huntington's disease (HD) or chorea is an autosomal dominant disorder with 100% penetrance, caused by an expansion of an unstable trinucleotide (CAG) repeat near the telomere of chromosome 4. The normal CAG repeat length in the gene is 35 or lower; expansions of 40 or more cause HD with complete penetrance. In successive generations, onset tends to develop earlier in life (correlating with longer repeat sizes—genetic anticipation).
- Age of onset is around 40 years. It progresses relentlessly over 15–17 years.
- Characterised by a triad of movement disorder, cognitive decline and behavioural changes.
- Main features are choreic movements and hypotonia. Rigidity may be seen in many cases.
- Personality and mood changes, psychosis and dementia are common.
- Oculomotor abnormalities occur in the form of slowing of saccades and increased response latency.
- No curative treatment is available. Symptomatic treatment is with dopamine-depleting agents, such as reserpine or tetrabenazine, and neuroleptics.

Athetosis

- Athetosis is slow writhing distal movements affecting fingers, hands, toes and feet (snake charmer's movement).
- Causes:
  - Kernicterus
  - Encephalitis
  - Previous cerebral infarcts
  - Degenerative brain disorders
- Treatment:
  - Haloperidol, tetrabenazine

Dystonia

- Dystonia is a movement disorder characterised by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. May be focal or generalised.
- Causes:
  - Kernicterus
  - Previous brain injury
  - Familial
  - Degenerative disorders
- Examples include cranial dystonia (blepharospasm or oromandibular or lingual dystonia), cervical dystonia (spasmodic torticollis), laryngeal dystonia (spasmodic dysphonia) and dystonic writer's cramp.
- Treatment:
  - Tetrabenazine, a dopamine-depleting drug.
  - High-dose anticholinergics (up to 24–30 mg of benzhexol/day; trihexyphenidyl up to 60–100 mg/day). Occasionally, L-dopa is useful in familial cases.
  - Sodium valproate (200–600 mg TID).
  - Botulinum toxin A and B for cervical dystonias.
  - Stereotactic thalamotomy or deep brain stimulation may be required if the disease is severe and distressing.

Hemiballismus

- It is violent flinging movements of the limbs. It is usually unilateral, and hence called hemiballismus.
- Cause:
  - Stroke affecting subthalamic nucleus (on contralateral side).
- Treatment:
  - Haloperidol 0.5–2.5 mg TID.
  - Tetrabenazine 25–50 mg TID.

Myoclonus

- Myoclonus is sudden, involuntary, brief, irregular, jerk-like contractions (positive myoclonus) or inhibition of contraction (negative myoclonus) of certain muscle groups. It may occur at two or more sites.
- Myoclonus may occur spontaneously, in response to sensory stimuli or with voluntary movements.
- Myoclonic muscle contractions are mostly accompanied by some movement of the affected body segment. In fasciculations or myokymia, twitches remain within affected body segment.
- Occasionally, myoclonus can be due to brief loss or inhibition of muscular tone, as in asterixis—for example, in hepatic encephalopathy ("liver flap") or in uraemic encephalopathy. This is known as negative myoclonus.

- Causes:
  - Metabolic disturbances:
    - Post-hypoxic brain injury
    - Chronic renal failure
    - Chronic liver disease
    - Respiratory failure
    - Electrolyte imbalance
  - Encephalitis
  - Drug overdose
  - Tricyclic antidepressants
  - Lipid storage diseases
  - Creutzfeldt–Jacob disease
  - Myoclonic epilepsy
- Treatment:
  - Correction of underlying disease
  - Sodium valproate (300–1200 mg/day)
  - Clonazepam (0.5–10 mg/day)

Tics

- Abrupt, usually brief and often repetitive and stereotyped movements, which vary in intensity and are repeated at irregular intervals.
- Movements most often jerky.
- Patients usually have an inner urge that precedes the actual movement or a local feeling of discomfort in the region of the tic. These premonitory sensations are usually temporarily relieved by the occurrence of the tic.
- Tics are voluntarily suppressible for variable periods of time, but this usually occurs at the expense of mounting inner tension and an irresistible need to perform the tic, followed by a rebound burst of tics. Motor and phonic tics can persist during all stages of sleep.
- Many patients with childhood-onset tics have Tourette's syndrome, a genetic disorder typically manifested by a wide array of chronic, fluctuating, simple, and complex motor and phonic (vocal) tics. This syndrome also has several associated co-morbidities, such as attention-deficit disorder (with or without hyperactivity) and obsessive compulsive disorder.
- Drug treatment includes neuroleptic drugs (e.g. fluphenazine, and risperidone), tetrabenazine (a monoamine-depleting drug), topiramate and clonazepam.

Q. Define tremors. How do you classify tremors? Describe them briefly.

- Tremor is rhythmic alternate movement at a joint due to synchronous or alternate contraction of antagonistic muscles.
- It is differentiated from other involuntary movement disorders, such as chorea, athetosis, ballism and myoclonus by its repetitive, stereotyped movements of a regular amplitude and frequency.
- Tremor may be simple (when it occurs in a single plane) or compound (when it is multiplanar, e.g. pill-rolling tremor of Parkinson's disease).
- It may be physiological or pathological. Physiological tremor is a fine tremor occurring at a frequency of 8–12/second. Physiologic tremor is barely visible to the unaided eye and is symptomatic only during activities that require extreme precision. It is accentuated during anxiety, fever, thyrotoxicosis and use of adrenergic drugs. Pathological tremor occurs in thyrotoxicosis, hypoglycaemia, Cushing's syndrome, alcohol withdrawal, drug ingestion and several neurological conditions.

Drugs/Toxins Causing Tremors

• Adrenergic agonists	• Neuroleptics
• Valproic acid	• Nicotine
• Lamotrigine	• Theophylline
• Lithium	• Monoamine oxidase inhibitor
• Tricyclic antidepressants	• Cyclosporin A
• Antihistamines	• Alcohol withdrawal
• Thyroxine	• Caffeine
• Nifedipine	• Corticosteroids

- Tremors may occur at rest (static) or on movement (kinesiogenic or action). Kinesiogenic tremor or action tremor is any tremor that emerges during voluntary contraction of muscles. It may be intentional (cerebellar) or postural action type.

Rest or Static Tremor

- Rest tremor (static tremor) is maximal at rest and becomes less prominent or disappears with activity.
- It is typically seen in parkinsonism where it may be of pill-rolling type. It is often associated with bradykinesia and rigidity.

Postural Tremor

- Tremor is maximal when limb posture is actively maintained against gravity.
- It is reduced by rest and is not markedly enhanced during voluntary movements towards a target.
- It often occurs due to toxic and metabolic factors, or stress where the onset is relatively acute.
- Insidious onset of postural tremor indicates a benign or familial essential tremor. It affects hands in nearly all cases and frequently affects head, face/jaw, voice, tongue and lower limbs. Ethanol is surprisingly effective in reversing essential tremor temporarily.
- The two most often used drugs are non-selective β-blockers (for example, propranolol) and primidone. Other drugs are topiramate, gabapentin and alprazolam. Intramuscular injections of botulinum toxin type A into intrinsic hand muscles can be considered in medically resistant cases. Lastly, deep brain stimulation in the ventral intermedius nucleus of thalamus is effective in over 90% of patients.

Intention Tremor

- Intention tremor is a cerebellar sign.
- Classic intention tremor is produced by lesions in the cerebellum or in the brachium conjunctivum pathway from deep cerebellar nuclei (dentate, globose and emboliform) to contralateral ventrolateral thalamus. Stroke, multiple sclerosis and tumour may affect the cerebellum and cerebellar pathways causing tremor. Drug toxicity (e.g. phenytoin, sodium valproate and amiodarone) is another important cause to exclude.
- It is brought on by voluntary movement and seen as rhythmic side to side oscillation as the limb reaches closer to the target, and stops on completion of the intended movement.
- Proximal limb muscles are usually involved more than distal ones.
- Clinically identified during finger-nose or heel-knee tests.

Q. What are the various signs in cerebellar diseases.

- **Dyssynergia:** Difficulty in carrying out complex movements resulting in breaking of an act into its components.
- **Dysdiadochokinesia:** Inability to perform alternating movements smoothly and rapidly (e.g. asking the patient to tap the palm of one hand with the fingers of the other, then rapidly turn over the fingers and tap the palm with the back of them, repeatedly or asking the patient to supinate and pronate the hands rapidly).
- **Dysmetria:** Loss of ability to judge the distance, speed or power of movement. The act may be stopped before the target is reached or the patient overshoots the desired target (past-pointing during finger-nose test).
- **Intention tremor:** Discussed above.
- **Rebound phenomenon:** Inability to stop the movement of a body part when suddenly released after active resistance (e.g. when the patient is asked to flex his elbow against physician's resistance, and then the physician suddenly releases the patient's arm, the patient may strike his face with his hand).
- **Hypotonia:** The tone of muscles is reduced on the side of the lesion.
- **Pendular knee jerk:** The reflexes tend to be less brisk and rather slower in rise and fall producing pendular jerk at the knee (three or more swings at the knee when the knee reflex is elicited with patient in sitting position and the legs hanging from bedside).
- **Nystagmus:** Coarse nystagmus, worse on looking to the side of lesion with fast component towards the affected side.
- **Titubation:** Rhythmic oscillation of head on the body or of the body itself. The patient may not sit or stand because of this and may fall backwards.
- **Gait ataxia:** Patient reels from side to side with a tendency to fall on the side of lesion. He cannot walk on a line (impaired tandem walking). If asked to walk around a chair, patient sways on the side of the lesion.
- **Speech disturbances:** Scanning (incoordination of tongue) or staccato speech (incoordination of the larynx) due to incoordination of the muscles of articulation. In staccato speech each syllable is uttered separately. In scanning speech, syllables of words are separated by pauses.

Q. Write a short note on cerebellar ataxias.

- Comprise a wide spectrum of neurological disorders with ataxia as the main symptom.
- Ataxia results from the involvement of cerebellar structures, or from a combination of cerebellar and extracerebellar lesions, especially due to brain-stem involvement or sensory involvement.

Classification

Acquired or sporadic ataxias
- Multiple system atrophy (MSA)
- Stroke (infarction, haemorrhage)
- Toxin-induced ataxias:
    - Ethanol
    - Drugs (antiepileptic agents, lithium, antineoplastics, cyclosporine, metronidazole)
    - Heavy metals
    - Solvents
- Immune-mediated:
    - Multiple sclerosis
    - Cerebellar ataxia with anti-glutamic acid decarboxylase (GAD) antibodies
    - Miller–Fisher syndrome
    - Systemic lupus erythematosus
    - Paraneoplastic syndrome (small-cell lung cancer, breast or ovarian cancer and lymphoma)
- Infectious/parainfectious diseases:
    - Cerebellar abscess
    - Chickenpox
- Traumatic
- Neoplastic disorder:
    - Cerebellar tumour
    - Metastatic disease
- Hypothyroidism
- Chiari malformations

Hereditary ataxias
- Autosomal dominant cerebellar ataxias:
    - Spinocerebellar ataxias
    - Episodic ataxias
- Autosomal recessive cerebellar ataxias:
    - Friedreich ataxia
    - Abetalipoproteinaemia
    - Ataxia telangiectasia

Hereditary Cerebellar Ataxias

- A heterogeneous group of neurological disorders, characterised by imbalance, progressive gait and limb incoordination, dysarthria, and disturbances of eye movements. Additional neurological and systemic features are usually present in these patients.

Spinocerebellar Ataxias

- Autosomal dominant.
- Progressive disorders in which the cerebellum slowly degenerates, often accompanied by degenerative changes in brain stem and other parts of CNS, and less commonly the peripheral nervous system.
- Several types of spinocerebellar ataxias (SCAs); SCA1 is the most common type.
- Ataxia is usually of cerebellar type, but in some SCAs, predominant or a strong sensory ataxia.
- Patients with SCA1 suffer from a progressive cerebellar syndrome with ataxia of gait and stance, ataxia of limb movements, dysarthria and cerebellar oculomotor abnormalities.
- Additional non-cerebellar signs in majority of patients.
- About half of the patients have supranuclear or nuclear gaze paresis and/or saccade slowing.

- Pyramidal tract signs with spasticity, extensor plantar responses, hyperreflexia, decreased vibration sense and dysphagia also common.

Friedreich Ataxia

- Autosomal recessive.
- Onset is early; typically presents in children aged 8–15 years and almost always presents before age 25 years.
- Progressive gait and limb ataxia, dysarthria, absent deep tendon reflexes, loss of joint position and vibration senses, and pyramidal weakness with extensor plantars.
- Ataxia is due to both posterior column involvement and spinocerebellar tract involvement.
- Hypertrophic cardiomyopathy in many patients.
- Axonal sensory neuropathy, distal wasting, scoliosis, sensorineural deafness, optic atrophy and diabetes are common features.

Q. Describe the normal CSF in adults.

• Colour	Clear, transparent	• Sugar	40–70 mg (2/3 of random blood sugar)
• Pressure	60–150 mm of CSF	• Cells	0–5 (lymphocytes)
• Proteins	20–40 mg%		

Q. Classify meningitis and enumerate its causes.

Classification

1. Bacterial meningitis
- Common organisms:
  - *Streptococcus pneumoniae* (30–50%)
  - *Neisseria meningitidis* (10–35%)
  - *Haemophilus influenzae* type B (1–3%)
- Uncommon organisms:
  - *Staphylococcus aureus*
  - *Staphylococcus epidermidis*
  - Group B streptococci
  - *E. coli*
  - *Klebsiella*
  - *Proteus* spp.
  - *Citrobacter* spp.
  - *Pseudomonas* spp.
  - *Listeria monocytogenes*

2. Tuberculous meningitis (TBM)
- *Mycobacterium tuberculosis*

3. Viral meningitis (aseptic meningitis)
- Enteroviruses (*Coxsackie*, poliovirus)
- Arboviruses
- HIV
- Herpes simplex-2
- Mumps virus

4. Spirochaetal
- Leptospirosis
- Lyme disease
- Syphilis

5. Rickettsial
- Typhus fever

6. Protozoal
- *Naegleria*

7. Fungal
- Cryptococcosis

8. Sarcoidosis

9. Malignant disease
- Leukaemic meningitis

10. Subarachnoid haemorrhage (SAH)
(causes meningismus)

11. Other non-infectious causes (see below)

- Other non-infectious causes include the following:
  - Vasculitis
    - Primary central nervous system vasculitis
    - Churg–Strauss syndrome
    - Wegener granulomatosis

- Connective tissue disease
  - Systemic lupus erythematosus
  - Rheumatoid arthritis
  - Sjögren syndrome

Q. Discuss the aetiology, clinical features, investigations and treatment of pyogenic meningitis. Syn: acute bacterial meningitis (ABM).

Aetiology

- Discussed in the Box given above.

Introduction

- Acute bacterial meningitis is an inflammation of the leptomeninges (arachnoid and pia), and fluid residing in the space that it encloses and also that in the ventricles of the brain. As the subarachnoid space is continuous around the brain, the spinal cord and the optic nerves, an infective agent gaining entry to any part of it may extend immediately to all of it, even its most remote recesses. Therefore, meningitis is always cerebrospinal. It also reaches the ventricles, either directly or by reflux through the basal foramens of Magendie and Luschka.
- Meningitis may be acute meningitis (with onset over hours to days) or chronic meningitis (syndrome persisting more than 4 weeks). Partially treated pyogenic meningitis may present with chronic meningitis.
- Inflammation of the meninges sometimes extends into the parenchyma with resultant symptoms and signs of cerebral or spinal cord involvement, often termed meningoencephalitis or meningoencephalomyelitis.
- *N. meningitidis* are Gram-negative, bean-shaped aerobic diplococci. Most infections are caused by organisms belonging to sero-groups A, B, C, Y and W-135. Sero-groups A and C predominate throughout Asia including India. The human naso-oropharyngeal mucosa is the only natural reservoir of *N. meningitidis*. Meningococci are transferred from one person to another by direct contact or via droplets.

Predisposing Factors

Pneumococcal Meningitis

• Acute otitis media	• Multiple myeloma
• Mastoiditis	• Immunoglobulin deficiency
• Pneumonia	• Splenectomy
• Diabetes mellitus	• Renal transplantation
• Recent head injury	• Bone marrow transplantation
• Sickle-cell disease	• Chronic alcoholism
• Hodgkin's lymphoma	

H. influenzae Meningitis

• Anatomic defects like dermal sinus tract and old skull fracture	• Diabetes mellitus
• Abnormality of immune defences	• Alcoholism

N. meningitidis Meningitis

- *N. meningitidis* meningitis occurs more often in patients with underlying immunodeficiency disorders and deficiency of any of the complement components.

Listeria monocytogenes Meningitis

- It has become an important pathogen, especially in elderly, debilitated and those who are immunosuppressed (transplantation, cancer therapy and connective tissue disorders). Alcoholism and high-dose steroids predispose to this. Infection is acquired by ingesting foods contaminated with this organism. Mortality rate is very high.

Others

- Neurosurgical procedures are followed by *S. aureus* meningitis. *S. epidermidis* meningitis follows cerebral ventricular shunt infections.

Pathogenesis

- All three important organisms are normal inhabitants of nasopharynx. Antecedent viral infections of the upper respiratory tract or lungs predispose the colonised patient to bloodstream invasion, which is the usual route by which bacteria reach the meninges. Once blood-borne, pneumococcus, meningococcus and *H. influenzae* have a predilection for meninges. Transnasal spread through cribriform plate to subarachnoid space may be important.
- Disruption of blood-CSF barrier by trauma, circulating endotoxin or an initial viral infection of the meninges also facilitates the entry of bacteria into subarachnoid space.
- A critical event after invasion is the inflammatory reaction produced by the invading bacteria. This results in production of several cytokines of which the most important are interleukin-1 and tumour necrosis factor. Many of the neurologic manifestations and complications of bacterial meningitis are due to the immune response to the pathogens rather than from direct pathogen-induced tissue injury. This factor is important in the treatment of acute bacterial meningitis (see treatment).

Clinical Features

- Fever, headache and vomiting are the cardinal features.
- Seizures, impairment of consciousness, photophobia, stiff neck and stiff back.
- Three patterns of onset are documented:
  - Fulminant onset—patient becomes seriously ill within 24 hours, without antecedent respiratory tract infections (25%).
  - Meningitis developing over 1–7 days and associated with respiratory symptoms (50%).
  - Meningeal symptoms after 1–3 weeks of respiratory symptoms (20%).
- In elderly, immunocompromised and debilitated patients, the classic signs of meningitis may be minimal, where low-grade fever and changes in mental status may occur without headache or neck rigidity.
- Meningococcal meningitis usually occurs as outbreaks. The evolution is extremely rapid and the onset is attended by petechial or purpuric skin eruptions, large ecchymoses and lividity of the skin of the lower parts of the body. Circulatory collapse may occur.
- Pneumococcal meningitis is usually preceded by an infection in the lung, ear or sinuses. Heart valves may be affected.
- *H. influenzae* meningitis follows upper respiratory tract infections and ear infections in young.

Signs of Meningeal Irritation

- Neck stiffness (neck rigidity)—The examiner is unable to put the patient's chin on the chest by passive flexion of the neck (due to neck muscle spasm).
- Kernig's sign—If the patient's thigh is flexed to 90° from the abdomen, it is then impossible to straighten the knee to more than 135° passively owing to spasm of hamstrings. This manoeuvre stretches roots of the sciatic nerve that are inflamed at their exits from the spinal theca.
- Brudzinski's neck sign—With the patient supine the physician places one hand behind the patient's head and places the other hand on the patient's chest. The physician then raises the patient's head (with the hand behind the head) while the hand on the chest restrains the patient and prevents the patient from rising. Automatic flexion of both the legs at hip and knee is a positive sign.
- Brudzinski's leg sign—On passively flexing one lower limb the other leg gets flexed automatically.

Investigations

- Increased total leucocytes , polymorphonuclear leucocytosis and raised ESR.
- Cerebrospinal fluid studies shown in the box.

- Appearance is turbid
- Pressure is elevated above 180 mm H_2O
- Cell count is raised, ranging from 5000 to 20,000/mL, neutrophil leucocytes predominate
- Protein level is elevated (more than 45 mg/dL)
- Sugar level is decreased (less than 40 mg/dL or less than 40% of blood sugar)
- Gram's stain of the sediment of CSF may show meningococci as Gram-negative, kidney-shaped, intracellular diplococci (inside neutrophils), and pneumococci as Gram-positive diplococci
- Culture of CSF grows the pathogen in 70–80% of cases
- Measurement of bacterial antigen in the CSF (Latex agglutination test)
- Limulus amoebocyte lysate assay detects Gram-negative endotoxin in CSF and is highly sensitive

- Hyponatraemia due to SIADH.
- Blood urea is elevated due to dehydration.
- Blood culture may be positive for *H. influenzae*, meningococci or pneumococci.
- Culture of pus from middle ear or sinuses.
- Biopsy of skin lesions (if present) to demonstrate meningococci.
- Radiography:
  - Radiograph of chest for pneumonia and lung abscess
  - Radiograph of skull for chronic osteomyelitis and fracture
  - Radiograph of paranasal sinuses for sinusitis
  - Radiograph of mastoids for mastoiditis
- CT scan may detect evidences of cerebritis, vascular occlusion, encephalomalacia, hydrocephalus, brain abscess or subdural empyema. Commonest CT finding is increased contrast enhancement of meninges.

Note: A lumbar puncture is safe in patients with suspected meningitis who are conscious, and have no papilloedema or focal deficits. In such cases lumbar puncture may be performed without a CT scan. Risk factors for elevated ICP include new-onset seizure, immunocompromised patient, decreased level of alertness, papilloedema or focal neurologic signs. A CT should be done in these patients before performing a lumbar puncture. However, if a CT scan is required to be done to exclude some other cause the patient must receive a dose of antibiotics and steroids before the CT scan.

Treatment

- Initial management includes airway protection and oxygenation, volume resuscitation, prevention of hypoglycaemia, control of seizures, reduction of hyperthermia and measures to reduce ICP and maintain CBF. The latter measures include elevation of head, fluid restriction, mannitol and hyperventilation.

Antibiotics

- Antibiotics must be administered immediately in patients with suspected meningitis. One should not wait for the results of lumbar puncture or CT scan of brain before administering antibiotics.
- The duration of treatment is 10–14 days.

Empiric Antibiotic Therapy for Bacterial Meningitis

Age group	Likely organisms	Empirical treatment (dose/day)
• Neonates	*E. coli*, β-haemolytic streptococci, *Listeria*	Ampicillin (100–150 mg/kg) plus cefotaxime (50 mg/kg) or ceftriaxone (50–100 mg/kg)
• Children (<12 years)	*H. influenzae*, *N. meningitidis*, *S. pneumoniae*	Ceftriaxone (or cefotaxime) plus vancomycin (40 mg/kg)
• Adults	*N. meningitidis*, *S. pneumoniae*	Ceftriaxone (or cefotaxime) plus vancomycin (40 mg/kg)
• Elderly or immunocompromised	*S. pneumoniae*, *Listeria*, Gram-negative organisms	Ampicillin plus ceftriaxone or cefotaxime or ceftazidime plus vancomycin

- Ceftriaxone is the drug of choice in any patient with acute meningitis when empirical treatment is required or the aetiological agent has been found to be one of these three common pathogens. However, many of the penicillin-resistant pneumococci have reduced susceptibility to third-generation cephalosporins; therefore, empirical management of meningitis should include vancomycin plus cefotaxime or ceftriaxone.
- For children who are less than 1 month old, consider adding vancomycin to the usual antibiotic combination of a broad-spectrum cephalosporin and ampicillin.
- In patients with impaired cell-mediated immunity (such as HIV, lymphoma, corticosteroid use or cytotoxic chemotherapy) there is an increased risk for *L. monocytogenes* and Gram-negative bacilli. Ampicillin and ceftazidime (or ceftriaxone or cefotaxime) should be used to ensure coverage for these, in addition to vancomycin for *S. pneumoniae*.

Pneumococcal and Meningococcal Meningitis

- Penicillin G, 20–24 million units/day in four to six divided doses IV for 10 days.
- Chloramphenicol 4–6 g/day in divided doses IV.

H. influenzae Meningitis

- Ampicillin 8–12 g/day in divided doses plus chloramphenicol 3–4 g/day in divided doses, both IV.

Steroids

- Despite antibiotics, serious complications can occur in patients with meningitis. Corticosteroids have been found to reduce the incidence of hearing impairment in children with *H. influenzae* meningitis. They have also been found to be useful in adults with pneumococcal meningitis. Because it is often difficult to distinguish patients who have bacterial meningitis from those with viral meningitis in the emergency room and because data indicate that it is preferable to administer dexamethasone before initiation of antibiotic therapy, most patients with suspicion of meningitis should receive steroids in the emergency room itself.
- Dexamethasone is given in a dose of 0.15 mg/kg every 6 hourly for 4 days.
- Adjunctive dexamethasone should not be used in patients who have already received antimicrobial therapy.

Complications

- Approximately 50% of adults with meningitis develop CNS complications including cerebrovascular involvement, cranial nerve palsies, focal neurological deficits, cerebral oedema and hydrocephalus.
- Pneumonia and otitis media are frequently seen in patients with meningitis.
- Systemic complications include septic shock, acute respiratory distress syndrome and disseminated intravascular coagulation.

Prophylaxis

N. meningitidis Meningitis

- Indications: Chemoprophylaxis is indicated in close contacts of patients with *N. meningitidis* meningitis. Administer it as soon as possible, preferably within 24 hours.
- Chemoprophylaxis regimens:
  - Rifampicin 10 mg/kg twice a day for 2 days. It is effective in about 95% cases.
  - Ceftriaxone 125 mg intramuscularly if age is less than 15 years, otherwise 250 mg. It has 97% efficacy.
  - Ciprofloxacin 500 mg orally (single dose) is also effective.
- Vaccine:
  - The quadrivalent polysaccharide vaccine that provides protection against sero-groups A, C, Y and W-135 and the bivalent polysaccharide vaccines (A and C) are available.
  - Vaccination, for both adults and children older than 2 years is carried out by administering single 0.5-mL dose, subcutaneously.

H. influenzae Meningitis

- Indications: Prophylaxis for meningitis caused by *H. influenzae* type B is recommended for all household contacts when at least one contact is less than 4 years old.
- Chemoprophylaxis regimen:
  - Rifampicin is given for prophylaxis though its efficacy is not clear.

Q. What is meant by Mollaret's meningitis?

- A syndrome of recurrent aseptic, self-limiting meningitis, characterised by large atypical monocytes (Mollaret cells) in the CSF.
- The cause is not known, but may be due to some virus infection.
- Characterised by repeated self-limiting episodes of fever, meningismus and severe headache (usually of 2–5 days duration) separated by symptom-free intervals.
- Most common aetiological agent is herpes simplex-2.
- Diagnosis can be made by PCR testing for HSV DNA in CSF.

Q. Write a short note on aseptic meningitis.

- Aseptic meningitis is inflammation of the meninges with CSF lymphocytic pleocytosis and no cause apparent after routine CSF stains and cultures. It does not typically cause notable parenchymal involvement of the brain (encephalitis) or spinal cord (myelitis). It has a more benign clinical course compared with either bacterial meningitis, meningoencephalitis or encephalomyelitis.
- Viruses (e.g. herpes simplex virus, varicella zoster virus, HIV, and enteroviruses) are the most common cause. Other causes may be infectious (rickettsiae, spirochetes, parasites, etc.), and non-infectious (vaccine reactions—rabies, pertussis; drugs—azathioprine, carbamazepine, ciprofloxacin, isoniazid, naproxen, ibuprofen, etc; malignancies—lymphoma, leukaemias; sarcoidosis, Behcet's disease, SLE, reaction to intrathecal drugs, etc.).
- Some may be asymptomatic but with CSF abnormalities.
- Symptoms include fever, headache, vomiting and meningeal signs.
- The CSF shows mildly or markedly elevated pressure and presence of 10 to >1000 lymphocytes/μL. Occasionally, a few neutrophils appear during the first few hours of viral meningitis. CSF glucose is normal and CSF protein is normal or mildly elevated. CSF may also be sent for viral culture, viral PCR and virus-specific antibodies.
- Viral aseptic meningitis is usually self-limited.
- Treatment is symptomatic.

Q. Enumerate the causes of neck stiffness.

• Meningitis	• Neck trauma (fracture, dislocation of cervical spine, sprain, rupture of ligament, etc.)
• Meningism	• Tetanus
• Leukaemic meningitis	• Rupture of intracerebral abscess into subarachnoid space
• SAH	• Elderly people
• Cervical spondylosis	

- The term "meningism" refers to symptoms that mimic those of meningitis but without inflammation of the meninges.

Q. Describe the causes, clinical features, investigations, differential diagnosis and sequelae of viral encephalitis.

- Encephalitis is a non-suppurative inflammation of brain caused by an inflammatory process.
- The inflammatory process can also involve the spinal cord (encephalomyelitis).

Viruses Causing Encephalitis

• Enteroviruses	• Arboviruses
• Herpes simplex (usually type 1)	• Rabies virus
• Mumps virus	• AIDS virus
• Influenza virus	• Lymphocytic choriomeningitis virus
• Japanese encephalitis virus	

- The most common virus responsible for large-scale epidemics in India is Japanese B encephalitis virus. It is spread by the mosquito *Culex tritaeniorrhynchus* that breads extensively in rice ecosystem. The pigs act as the amplifying hosts. Humans are incidental to the transmission cycle.
- In immunocompetent adults, >90% of cases of herpes simplex encephalitis (HSE) result from infection with HSV-1, with the remainder due to HSV-2 infection. More than two-thirds of cases of encephalitis due to HSV-1 appear to result from reactivation of endogenous latent HSV-1 in individuals previously exposed to the virus.
- Influenza virus is an important cause of encephalitis, mostly seen in children.

Clinical Features

- Clinically characterised by association of encephalopathy, focal deficits, seizures and fever.
- Viral encephalitis is often preceded by non-specific features (fever, myalgias, and arthralgias).

- Onset is acute with fever and headache, similar to acute meningitis but with accompanying features of cerebral involvment. Cerebral features include variable degree of change in consciousness, confusion, disorientation, mental changes such as delirium, agitation, hallucinations with focal signs such as hemiplegia, aphasia, cranial nerve deficits and involuntary movements. Seizures and raised ICP are common. Many show signs of meningeal irritation. Specific clinical signs may occur depending on particular virus, e.g. rabies virus predominantly affects brain stem and limbic system early in the course. Herpes simplex virus has affinity to involve temporal and frontal lobes.
- Associated myelitis may lead to flaccid, asymmetric paralysis of the limbs along with sensory changes and bladder involvement. This must be differentiated from acute epidural abscess.
- Additional features particularly seen in Japanese encephalitis include parkinsonian syndrome with mask-like facies, tremor, cogwheel rigidity and choreoathetoid movements.

Herpes Simplex Viral Encephalitis

- It is important to suspect this condition as it is potentially treatable.
- Although there are no clinical features that are pathognomonic for HSVE, predilection of the virus for temporal and orbitofrontal lobes results in characteristic clinical picture that should alert the clinician to the condition. A 1 to 4-day history of gradually increasing headache and fever is followed by alteration of consciousness, memory loss, personality changes, confusion, disorientation and olfactory hallucinations. Focal neurologic signs such as hemiparesis, aphasia, focal or generalised seizures and signs of meningeal irritation may also be present.

Investigations

- CT scan is usually normal in encephalitis. In HSE, it may show low attenuating areas, particularly in the temporal lobes with surrounding oedema. In Japanese encephalitis, lesions in thalamus are common.
- Cerebrospinal fluid:
  - Clear.
  - Increased pressure.
  - Protein levels are mildly elevated (70–700 mg/dL; values >800 mg/dL rarely seen).
  - Sugar is normal or mildly reduced.
  - Cell count is increased (usually 5–500/mm^3) and is lymphocytic. RBSs are common in herpes simplex encephalitis.
  - Antibodies to specific virus in increasing titres are seen if serial examinations are done. It is useless for immediate diagnosis. IgM antibodies are important for early diagnosis.
  - PCR of CSF is the diagnostic method of choice for viral encephalitis including HSE and therapy should be instituted pending the results of PCR.
- EEG and MRI of brain are important in patients with suspected herpes encephalitis. In JE, T2-weighted images show increased signal over the thalamic region in most patients. Haemorrhagic lesions are found in 70% of patients; similar lesions are less commonly found over the cortex, midbrain, cerebellum and spinal cord.
- Brain biopsy in select patients.

Differential Diagnosis

- Viral encephalitis should be differentiated from acute metabolic encephalopathies, post-infectious encephalomyelitis, bacterial or tubercular infections of the brain, and stroke. This is possible from clinical examination, CT scan, CSF evaluation and blood biochemistry.

Post-Infectious Encephalomyelitis

- It indicates encephalitis that follows a viral illness without actual viral invasion of CNS or following administration of some vaccines. It is thought to be due to hypersensitivity reaction to viral or vaccinal proteins which results in demyelination.
- Rabies vaccine (Semple vaccine) and measles infection are most common causes of post-infectious encephalitis.
- Two forms are described: Acute disseminated encephalomyelitis (ADEM) and acute haemorrhagic leucoencephalitis (AHLE).

Acute Disseminated Encephalomyelitis (ADEM)

- The patient develops a multifocal inflammatory demyelinating process (acute disseminated encephalomyelitis— ADEM) after 1–3 weeks following infection or vaccination. The preceding infection is typically a benign upper respiratory tract infection or a non-specific febrile illness. Preceding infections consist mostly of various viral infections

(measles, varicella and rubella), group A β-haemolytic streptococci and intracellular bacteria such as *Mycoplasma pneumoniae*.

- This process involves cranial nerves (e.g. optic nerve), cerebrum, brain stem and spinal cord.
- ADEM appears to result from an immune-mediated attack against an antigen or antigens present in brain myelin.
- Characterised by acute onset (maximal neurological deficit reached within hours to days of onset) of focal neurological signs and encephalopathy (early evidence in the form of behavioural impairment, delirium and fluctuations of vigilance). Other features include fever and seizures.
- Key features that help in differentiating ADEM from encephalitis include a history of vaccination or a prodromal illness in the weeks preceding neurologic signs and symptoms. In ADEM, demyelination involving the optic nerve or spinal cord can result in monocular visual loss, symptoms of spinal cord dysfunction (paraplegia or tetraplegia with deep tendon reflexes abolition and acute urinary retention) or acute polyradiculoneuropathy, which are generally rare in acute encephalitis.
- MRI in ADEM typically shows multifocal lesions with a predilection for the white matter in both hemispheres and infratentorial areas, whereas acute encephalitis usually produces lesions that involve both grey and white matter.
- CSF profiles are similar in ADEM and acute viral encephalitis. Oligoclonal bands should be sought in patients with a presumed diagnosis ADEM as multiple sclerosis can present with similar features.
- Treatment is usually with high-dose intravenous corticosteroids alone or together with other immunomodulatory therapies, including intravenous immunoglobulin or plasma exchange.

Acute Haemorrhagic Leucoencephalitis (AHLE)

- In contrast to ADEM, AHLE has a fulminant course with haemorrhagic white matter lesions.
- Onset is acute, with fever, coma, seizures and focal neurological signs.
- CSF opening pressure is usually elevated and analysis shows a lymphocytic pleocytosis and up to 1000 red blood cells/mL with increased protein levels, ranging from 100 to 300 mg/dL.
- MRI shows widespread hyperintensities in white matter on both T1- and T2-weighted images.

Management

- General measures to care for the unconscious patient should be started. Anticonvulsants are often necessary. Brain oedema is best controlled with dexamethasone 4 mg 6 hourly.
- Herpes simplex encephalitis responds well to acyclovir (10 mg/kg IV 8 hourly for 14–21 days), if instituted early. As the drug is safe, it may be given to all patients with diagnosis of viral encephalitis as specific diagnosis is made only later or is impossible. However, drug is too expensive. It can also produce renal insufficiency.
- Oseltamivir in influenza-associated encephalitis.

Prognosis

- Highly variable. In large epidemics high mortality is seen. Many may be left with residual deficit like dementia, focal deficits and epilepsy. Other sequelae include cerebellar and extrapyramidal signs, flexion deformities of the arms, hyperextension of the legs, language impairment, learning difficulties and behavioural problems. Many recover completely if the illness is mild.

Vaccines

- Two vaccines against Japanese encephalitis are available: An inactivated mouse brain-derived vaccine and a live-attenuated vaccine (produced in hamster kidney cells or Vero cells).
- Mouse brain-derived vaccine can produce local as well systemic allergic reactions. It can occasionally produce moderate to severe neurologic symptoms, including encephalitis, seizures, gait disturbances and parkinsonism.

Q. Describe the aetiology, clinical features, complications and treatment of herpes zoster.

Aetiology

- Herpes zoster is the result of reactivation of varicella zoster virus (VZV) lying dormant in the dorsal root ganglion following chicken pox in early life. This may occur spontaneously or with immunosuppression by other diseases, when it can be severe and widespread (e.g. use of steroids, and HIV infection).

Clinical Features

- Symptoms and signs are dermatomal in distribution. The dermatomes from T3 to L3 are most commonly involved although cranial nerves may also be involved.
- First manifestation is pain in the involved dermatome.

- In 3–4 days skin becomes red and vesicles appear. Vesicles dry up in a week's time leaving scars.
- Pain, which is severe and burning in nature, persists as long as vesicles remain.
- Herpes over face usually involves the first division of Vth nerve and occasionally VIIth nerve (Ramsay-Hunt syndrome).
- Some individuals may only present with prodromal symptoms, never developing the telltale rash. This phenomenon is known as "zoster sine herpete."
- Multidermatomal involvement or dissemination is seen in immunocompromised patients.

Complications

- When Vth nerve gets involved, cornea is affected. If appropriate care is not taken, it may get damaged permanently.
- Sometimes, pain persists indefinitely even after the vesicles have dried up. When pain persists even after 4–6 weeks, it is called postherpetic neuralgia. The risk for postherpetic neuralgia increases with age, and almost half of patients over 60 years who experience herpes zoster will develop it, immunocompromised patients being more susceptible.
- Other potential complications include encephalitis, myelitis, meningitis and peripheral nerve palsies.

Diagnosis

- The diagnosis is mainly clinical.
- The polymerase chain reaction (PCR) technique is the most sensitive and specific diagnostic test, as it can detect VZV DNA in fluid from the vesicle. It can be used if diagnosis is not clear.

Treatment

- Idoxuridine 5% lotion over the skin or 0.1% solution for corneal instillation.
- Oral aciclovir (800 mg five times daily), famciclovir (500 mg three times daily) and valaciclovir (1 g three times daily) are useful in early stage of disease. They also reduce development of postherpetic neuralgia.
- Pain is controlled with analgesics.
- Calamine lotion is applied as a smoothening agent.
- Postherpetic neuralgia may become very refractory but may respond to carbamazepine or amitriptyline or gabapentin or pregabalin.

Q. Discuss the aetiopathogenesis, clinical features, complications and management of tuberculous meningitis (TBM).

Aetiopathogenesis

- Tuberculous meningitis (TBM) is infection caused by *Mycobacterium tuberculosis*.
- It may occur as part of widespread haematogenous spread of mycobacteria in children. However, in most cases, it occurs by reactivation of a subpial focus of a dormant lesion (Rich's focus).

Pathology

- Subarachnoid space throughout CNS is involved. Basal cisterns and sylvian fissure are maximally involved.
- Thick exudates cover the base of the brain and scattered tubercles are found in the meninges. This may lead to communicating hydrocephalus.
- Emerging cranial nerves are engulfed by these gelatin-like exudates.
- Exudates may also block foramina of Luschka and Magendie or any point of CSF pathway resulting in non-communicating hydrocephalus.
- Blood vessels at base show inflammatory changes and may cause cerebral infarcts.
- Exudates can also surround lower part of spinal cord and cauda equine resulting in tuberculous radiculomyelopathy.

Clinical Features

- It has a subacute or chronic course. Disease may occur at any age, but children are commonly affected.
- In children, early manifestations are lack of interest, malaise, fever, anorexia, urinary retention and constipation.
- Classical meningitis symptoms seen are fever, headache and vomiting appearing over a few days. Signs include neck rigidity and positive Kernig and Brudzinski signs.
- Further on, cranial nerve palsies (commonly blindness, diplopia due to ophthalmoplegia, facial palsy and deafness) with hemiparesis or paraplegia follow. These deficits may occur suddenly due to vascular involvement.

- Features of increased ICP due to hydrocephalus will result in change in intellect, altered consciousness, urinary incontinence and gait ataxia.
- Seizures are common.
- Movement disorders like chorea, hemiballismus, athetosis, generalised tremors, myoclonic jerks and ataxia may occur.
- The syndrome of inappropriate antidiuretic hormone (SIADH) secretion is a common complication leading to hyponatraemia.
- If left untreated, patient lapses into vegetative state and dies.
- Tuberculous spinal meningitis may manifest as an acute, subacute or chronic form. The dorsal cord seems to be affected most commonly, followed by the lumbar and the cervical regions.
  - The clinical picture in primary spinal meningitis is often characterised by myelopathy, with progressive ascending paralysis, eventually resulting in basal meningitis and associated sequelae.
  - In some cases with acute onset, patients develop acute paraplegia with sensory deficit and urinary retention.
  - The subacute form is often dominated by myeloradiculopathy with radicular pain and progressive paraplegia or tetraplegia.
  - A less virulent chronic form might mimic a very slowly progressive spinal cord compression or a non-specific arachnoiditis.

Differential Diagnosis

- Partially treated pyogenic meningitis.
- Cryptococcal meningitis (particularly in HIV positive patients).
- Syphylitic meningitis.
- Other rare infections (e.g. Brucella, and fungi).
- Neoplastic meningitis (leukaemia, lymphoma, metastasis; and CSF glucose very low).
- Miscellaneous (e.g. SLE, Behcet's disease, and sarcoidosis).

Investigations

CT Scan and MRI

- Meningeal enhancement.
- Presence of exudates.
- Hydrocephalus.
- Cerebral infarcts.
- Gadolinium-enhanced MRI more sensitive than CT.

CSF Findings in Tuberculous Meningitis (TBM)

- Pressure is increased.
- Usually clear, but xanthochromia suggests block in the CSF flow in the spinal canal.
- A fine clot or cobweb may form on allowing CSF to stand for some time.
- Protein levels are elevated (100–800 mg/dL). Very high levels indicate block to CSF flow.
- Sugar is lowered (to less than 40% of blood sugar).
- Cell counts are elevated and predominantly lymphocytic.
- Ziehl-Neelsen staining or fluorescent staining of the coagulum may show mycobacteria.
- Cultures are rarely positive and take 6 weeks.
- Adenosine deaminase levels (ADA) are elevated; however, no cut-off has been defined to differentiate TBM from pyogenic meningitis.
- Nucleic acid amplification tests (NAAT) on CSF—PCR tests to detect mycobacterial nucleic acids. The Xpert MTB/RIF assay uses real-time PCR.

Other Investigations

- Chest radiograph—It may show evidence of pulmonary tuberculosis (old or active) in 50% cases.
- Mantoux test (rarely useful).

Partially Treated Pyogenic Meningitis Versus Tuberculous Meningitis

- Following CSF features favour diagnosis of TBM:
  - Duration of illness 5 days

- Presence of headache
- CSF white blood cell count of 1000 per mm^3
- Clear appearance of CSF
- CSF lymphocyte count 30%
- CSF protein content of 100 mg/dL

Management

- Anti-TB chemotherapy should be started at the earliest. Early phase (first 2 months) involves intensive therapy combining rifampicin, INH, pyrazinamide and streptomycin or ethambutol. After a period of 2 months rifampicin with INH is continued for another 7–10 months. Ethambutol and streptomycin do not penetrate blood–brain barrier effectively.
- All patients should receive prednisolone 40 mg a day to reduce meningeal adhesions and severity of arteritis. It is given for 3 weeks followed by tapering over next 3 weeks.
- For communicating hydrocephalus, acetazolamide or furosemide. For non-communicating hydrocephalus, ventricular drainage or ventriculo-peritoneal shunt.

Prognosis

- If treatment is instituted early before neurological deficits appear, recovery may be complete. Presence of focal deficits and change in consciousness before therapy predict poor outcome. Residual deficits will include dementia, blindness, deafness, epilepsy, hemiparesis and paraparesis.

Q. What are the common causes of acute fever and altered sensorium (febrile encephalopathy)?

- Acute bacterial meningitis
- Tuberculous meningitis
- Viral encephalitis
- Acute disseminated encephalomyelitis
- Brain abscess
- Cortical venous thrombosis
- Cerebral malaria
- Leptospirosis
- Anticholinergic (e.g. dhatura) poisoning
- Heat stroke
- Sepsis-associated encephalopathy
- Neuroleptic malignant syndrome
- Serotonin syndrome

Q. Describe the clinical features and management of neurosyphilis.

- The organism (*Treponema pallidum*) invades nervous system within 3–18 months after primary infection.
- Initial event is asymptomatic meningitis. This may remain so and cause more damage later on.
- All forms of neurosyphilis have meningitis as a component, in variable severity.
- Vascular changes occur secondary to meningitis as endarteritis obliterans.

Asymptomatic Neurosyphilis

- Asymptomatic invasion of CNS by *Treponema* is common within a few months of primary infection.
- Diagnosis is made by demonstrating CSF lymphocytosis with elevated protein and positive VDRL test.
- This is found in nearly 25% of cases with late latent form of syphilis. Many of these patients may go onto develop symptomatic neurosyphilis. .
- These patients should be treated with penicillin.

Symptomatic Neurosyphilis

- Although mixed features are common, the major categories are:
  - Meningeal syphilis
  - Meningovascular syphilis
  - Parenchymatous syphilis that includes general paralysis of insane and tabes dorsalis.

Meningeal Syphilis

- Symptoms of meningitis may occur at any time after infection, but appears usually within 2 years.
- Symptoms consist of headache, stiff neck, cranial nerve palsies, convulsions and mental confusion.

- Papilloedema with symptoms of increased ICP may occur.
- Patient is afebrile. CSF is abnormal.
- May have skin rash on palms and soles.

Meningovascular Syphilis

- Presents usually 6–7 years after initial infection, but can be as early as 6 months to as late as 10–12 years.
- Should be suspected whenever a young patient presents with stroke resulting in hemiparesis, aphasia, visual loss, etc. Features of stroke are generally subacute in nature. Other features are headache, vertigo, insomnia and psychological abnormalities.

CSF Findings

• Pressure may be normal or raised	• Cell count is mildly elevated and is lymphocytic
• Fluid is clear	• Gamma globulin levels are elevated
• Protein is elevated (100–200 mg%)	• VDRL and FTA-ABS (fluorescent treponemal antibody absorption) are positive
• Sugar is normal	

- The gold standard for diagnosis is VDRL from CSF, which is highly specific but only 30–70% sensitive for neuro-syphilis. CSF FTA-ABS is more sensitive but not specific because false positives are common.

General Paralysis of Insane

- It develops 20 years after primary infection.
- This is due to diffuse involvement of parenchyma producing a variety of manifestations which include personality changes, illusions, delusions, hallucinations, reduced memory, hyperactive reflexes and Argyll Robertson pupils.

Tabes Dorsalis

- Tabes is the parenchymal form of neurosyphilis that involves posterior columns in the spinal cord.
- Usually develops 20–25 years after onset of infection.
- Symptoms are severe lightening pains in trunk and extremities, ataxia and urinary incontinence.
- Signs include variable patchy tactile sensory loss and severe impairment of proprioception with sensory ataxia. Tendon jerks are absent. Muscular strength is normal. Trophic lesions, perforating ulcers of feet and Charcot joints are complications. Argyll Robertson pupils occur in tabes dorsalis also.
- Visceral crisis consisting of abrupt epigastric pain with vomiting lasting for hours occur. Barium studies show pyloro-spasm (gastric crisis). Similarly, intestinal crisis with diarrhoea, rectal crisis with tenesmus, genitourinary crisis with strangury and pharyngeal–laryngeal crisis with gulping movements and dyspnoea may occur.
- CSF findings—as described previously.

Treatment

- Penicillin is the drug of choice. Dose is 18–24 million units/day for 15–20 days.
- If patient is sensitive to penicillin, erythromycin and tetracycline 0.5 g 6 hourly for 20–30 days is recommended.

Follow-Up

- Patient should be re-examined every 3 months and CSF at 6 months interval. If CSF is normal and VDRL titres have come down no further treatment is required. If CSF remains abnormal, another full course of penicillin should be given.

Q. Discuss briefly about Charcot joint.

- Charcot joint is the complication of chronic loss of proprioception and pain senses from lower extremities.
- Common causes include chronic severe sensory polyneuropathies (e.g. diabetes mellitus, leprosy and toxins), syringo-myelia and tabes dorsalis.
- Most frequently, hips, knees and ankles are affected. Occasionally, lumbar spine and upper limb joints are affected.
- Begins as osteoarthritis with repeated injuries to the insensitive joints, and progresses to destruction of articular surfaces.
- Often presents initially as a warm, swollen, and erythematous joint.
- Frequent subluxation fractures with mild discomfort and minimal pain may occur. The initial treatment is immediate immobilisation and avoidance of weight bearing is required in early stages. Further mechanical injury should be prevented.

Q. What are the common demyelinating diseases?

- Demyelination is the loss or destruction of the nerve's myelin coating in the central or peripheral nervous system (brain, spinal cord, optic nerves and nerves) resulting in impaired or loss of function of neurons.
- Schwann cells supply the myelin for peripheral neurons, whereas oligodendrocytes myelinate the axons of CNS.
- Symptoms and signs will depend on the area that is involved.

Common Causes of Demyelination

Demyelinating diseases of CNS	Demyelinating diseases of peripheral nervous system
- Multiple sclerosis - Neuromyelitis optica - Infectious—acute disseminated encephalomyelitis (ADEM), HIV encephalitis, progressive multifocal leucoencephalitis, subacute sclerosing panencephalitis, Creutzfeldt–Jakob encephalitis - Nutritional—Wernicke encephalopathy, subacute combined degeneration - Toxic—radiation, chemotherapeutic agents, toluene, mercury, methanol - Hypoxic/ischaemic—vasculitis, posterior reversible encephalopathy syndrome	- Dry beriberi - GB syndrome - Chronic inflammatory demyelinating polyneuropathy - Charcot–Marie–Tooth disease - Vitamin B_{12} deficiency - Organophosphate poisoning - Copper deficiency

Q. Describe the nerve supply of urinary bladder. Add a note on neurogenic bladder.

- Dysfunctions of bladder arising out of neurological disorders are termed neurogenic bladder.
- Bladder and its sphincters are innervated by sympathetic (from L1 and L2), parasympathetic (from S2, S3 and S4 segments) and somatic motor (pudendal nerve S2–S4) fibres. Lumbosacral centres are under control from pontomesencephalic and cortical micturition centres.
- Sympathetic fibres are inhibitory to the detrusor and allow urine to collect. Parasympathetic fibres are facilitatory and aid in emptying the bladder. Internal sphincter is in contracted state during rest and relaxes while micturating. External sphincter is under voluntary control. Cortical centre and its connection with frontal lobe control conscious aspects of micturition and have inhibitory influence over lower centre. Pontomesencephalic centre acts as a coordinator over entire afferent and efferent influences.

Somatic sacral roots — Spinal cord
Sympathetic nerves from L1 & L2 — S2 S4 — Parasympathetic outflow
Conus medullaris
Inferior hypogastric plexus — Pelvic nerves
Hypogastric nerves
Detrusor muscle
Pudendal nerve
Internal sphincter (part of detrusor muscle)
Urethra — External sphincter (skeletal muscle)

Nerve supply to the bladder and sphincters
+ Excitatory synapse   − Inhibitory synapse

- During the storage phase of micturition, bladder filling activates afferent nerve fibres in the bladder wall. This afferent input results in stimulation of sympathetic efferent activity (via the hypogastric nerve), leading to contraction of smooth muscles in the bladder base and proximal urethra (via activation of α-adrenergic receptors) and relaxation of the detrusor (via activation of β-adrenergic receptors in the bladder body). Somatic efferent activity (via the pudendal nerve) also increases, resulting in increased tone of the striated external urethral sphincter. These responses promote continence. Parasympathetic system is largely inactive during urine storage.
- The voiding phase of micturition is initiated voluntarily by signals from cerebral cortex. Initial event is relaxation of striated external urethral sphincter caused by inhibition of somatic efferent activity. There is inhibition of sympathetic efferent activity with concomitant activation of parasympathetic outflow to the bladder and urethra.

Neurogenic Bladder

- Neurogenic bladder dysfunctions are classified according to functional status of the bladder based on cystometry and urodynamic studies.
- Several patterns of bladder dysfunctions may arise. Basic principle involves consideration of detrusor (atonic or hypertonic) and sphincteric activity (coordinated or not with detrusor contraction).
- Lesions affecting sacral segments or peripheral autonomic fibres result in atonic bladder with loss of sphincteric coordination. This results in loss of detrusor contraction, difficulty in initiating micturition and overflow incontinence. Residual urine volume is increased. If a sensory neurogenic bladder is present, the affected individual may not be able to sense when the bladder is full. In the case of a motor neurogenic bladder, the individual will sense the bladder is full but the detrusor may not contract.
- Spinal cord disorders above lumbar segments result in hypertonic bladder with loss of sphincteric coordination. Symptoms include urgency, urge incontinence, incomplete voiding and increased residual urine.
- Lesions of cerebral hemispheres, if located post-centrally, result in loss of awareness of bladder fullness and cause incontinence, whereas pre-central lesions cause difficulty in initiating micturition. Residual urine is insignificant. More anteriorly located frontal lobe lesions cause loss of social inhibition resulting in unconcerned micturition at inappropriate places.
- Common causes include multiple sclerosis, parkinsonism, stroke, myelopathies, spinal cord injuries, spina bifida, diabetes mellitus with autonomic neuropathy, unintended sequelae following pelvic surgery, and cauda equina.
- Neurogenic bladder predisposes to development of urinary infection, back pressure changes at upper urinary tract and requires to be treated appropriately. Treatment requires correct assessment by urodynamic studies, followed by proper catheterisation techniques, use of pharmacological agents (anticholinergic drugs like oxybutynin for detrusor spasticity, α-adrenergic blockers like terazosin, if internal sphincter fails to relax) and surgery in certain cases. Botulinum toxin type A is useful in reducing episodes of urinary incontinence in patients with neurogenic detrusor overactivity.

Q. Describe the aetiology, clinical features, complications and management of paraplegia.

Q. Write a short note on paraplegia in flexion, paraplegia in extension, flaccid paraplegia and acute spinal paraplegia.

- Paraplegia is dense paralysis of both lower limbs. It is usually due to disorders of spinal cord. But occasionally it may be due to lower motor neuron disorders like GB syndrome, myopathies or an intracranial parasagittal lesion like meningioma or sagittal sinus thrombosis.

Spinal Causes of Paraplegia

- Acute	Trauma, transverse myelitis, multiple sclerosis, neuromyelitis optica, infarction of spinal cord (vasculitis, anterior spinal artery thrombosis), spinal epidural abscess
- Subacute or chronic	
- Spinal cord compression (extradural)	Spinal metastasis, tuberculosis of spine, primary bone tumours, disc prolapse or spondylosis at lower cervical region, ligamental hypertrophy in cervical region, extradural granulomas and neoplasms (usually lymphoma), extradural arteriovenous malformation
- Intraspinal tumours (Intradural extramedullary)	Meningioma (including parasagittal meningioma of brain), neurofibroma

• Intramedullary tumours (Intradural intramedullary)	Astrocytoma, ependymoma, syringomyelia
• Miscellaneous	Arachnoiditis, syringomyelia, radiation myelopathy, lathyrism, hereditary spastic tropical spastic paraplegia, subacute combined degeneration, fluorosis, HIV myelopathy, paraneoplastic, spinocerebellar ataxias, triorthocresyl phosphate (TOCP) poisoning, subacute myelopathic neuropathy (SMON), arsenic poisoning, radiation

• High cauda equina lesions (compressive) at L1 or L2 can cause paraplegia of lower motor neuron type.

Clinical Features

• Acute onset lesions result in flaccid, areflexic paralysis in both lower limbs and sensory loss till the level of lesion. Urinary retention is present. This phase of flaccid paralysis is due to spinal shock.
• Spinal shock gradually resolves and features of UMN lesion appear after 3-4 weeks.
• Spinal shock may persist for longer duration if infections occur or bed sores develop.
• Limbs may assume paraplegia in "flexion" or "extension" depending on the lesion.
  • When corticospinal tracts alone are affected the extrapyramidal system takes the upper hand, resulting in increased tone of antigravity muscles (paraplegia in extension).
  • When the influence of extrapyramidal system is cut off, the spinal arc takes over and there is relative increase in the tone of flexors of legs (paraplegia in flexion).
• Subacute or chronic spinal paraplegias appear as "spastic paraplegias".
• Presence of sensory and bladder symptoms and signs depends on the underlying cause.

Investigations

• Plain radiograph of the spine to detect vertebral diseases, fractures, etc.
• CSF in evaluation of arachnoiditis.
• Appropriate diagnostic tests to determine the underlying cause. These include CT scan and MRI of spine.

Complications

• Complications of paraplegia may lead to death.
• Common complications of paraplegia are given in the information box below.

• Pressure sore	• Faecal impaction with intestinal obstruction
• Urinary infection	• Contracture of limbs
• Renal calculi	

Management

• Care of paraplegia is as important as treating the underlying cause.

Skin

• Pressure sores have to be prevented as they occur due to loss of sensation and diminished blood supply.
• Patient should be turned every 2–4 hourly to a position that avoids pressure over bony prominences.
• Skin must be kept dry and clean.
• If possible, patient should be nursed on a specially designed mattress like water or air-cushioned bed.
• If pressure sores develop patient must not lie on the affected side. Aseptic care must be taken. Skin grafting may be necessary.

Bladder

• Aseptic intermittent catheterisation should be done.
• Indwelling catheter is not desirable as it predisposes to infection, reduces bladder capacity and promotes calculus formation.
• Occasionally, urinary diversion procedures maybe necessary.
• Urinary infections should be treated promptly. Fluid intake should be adequate.

Bowel

- Constipation is prevented by laxatives.
- If faecal matter becomes hard, manual evacuation is necessary.

Paralysis

- Spasticity can lead to contractures and flexor spasms.
- Regular passive movements of the limbs.
- Patient should be nursed in a posture that discourages flexion at joints.
- Drug treatment of spasticity is effective in many patients but it may reduce function as many patients use their spasticity as an aid to stand or walk. Baclofen is the most effective drug for reducing spasticity. Diazepam and tizanidine also work well in most patients.
- In severe cases, intrathecal baclofen maybe administered via a pump. If this is not effective, sectioning of the anterior roots (rhizotomy) maybe done.

Rehabilitation

- Patient can be taught to use a calliper or wheel chair.
- With encouragement patient can be made an active member of the society.

Q. Discuss the causes and differential diagnosis of spastic paraplegia.

- Spastic paraplegia denotes an upper motor neuron lesion causing paraplegia. It is invariably due to a lesion that appears subacutely or chronically. Acute lesions generally cause flaccid paralysis.
- The term "ataxic paraplegia" is used when ataxia is a predominant feature and is present with paraplegia (or paraparesis). Important causes include spinocerebellar degeneration and Friedreich's ataxia.
- Once spinal shock resolves in patients with acute causes of paraplegia (see under "spinal causes of paraplegia"), paraplegia with spasticity develops.

Causes of Spastic Paraplegia

Group	Causes
• **Pure motor syndromes** (motor disturbance alone)	Any early cord compression, motor neuron disease, hereditary spastic paraplegia, Erb's spastic paraplegia (syphilitic), lathyrism, residual deficit from acute lesions (on partial recovery)
• **With sensory and bladder involvement**	See under "spinal causes of paraplegia" above (subacute or chronic)

- In elderly, motor neuron disease, spinal metastasis and cervical spondylosis are the common causes.
- In younger age group hereditary spastic paraplegia, tuberculosis of spine, extradural granulomas and neurofibromas are the common causes.
- Hereditary spastic paraplegia has onset from early childhood to adulthood onwards, with insidious development of leg stiffness and/or abnormal wear of the shoes.
- Lathyrism and residual deficits from previous lesions occur at all age groups.
- Diagnosis maybe arrived at by adequate history, physical signs, CT scan, MRI and CSF analysis. Arteriovenous malformations may require spinal angiography. Tumours and granulomas require surgery and biopsy for adequate diagnosis and further management.
- In some patients, antispasticity drugs such as baclofen and tizanidine can be helpful to reduce spasticity.

Q. Describe briefly about transverse myelitis.

- Transverse myelitis (TM) is a heterogeneous group of inflammatory disorders characterised by acute or subacute motor, sensory and autonomic (bladder, bowel and sexual) spinal cord dysfunction. The term myelitis is a non-specific term for inflammation of the spinal cord; transverse refers to involvement across one level of the spinal cord. The term 'myelopathy' is a broad, generic term which does not imply any particular aetiology; myelitis refers to an inflammatory disease process.
- TM occurs with optic neuritis in neuromyelitis optica (Devic's disease).

Causes

- Parainfectious (occurring at the time of and in association with an acute infection or an episode of infection)
  - Viral: herpes simplex, herpes zoster, cytomegalovirus, Epstein–Barr virus, enteroviruses (poliomyelitis, Cox-sackie virus, echovirus), human T-cell leukaemia virus, human immunodeficiency virus, influenza, rabies
  - Bacterial: Mycoplasma, Lyme borreliosis, syphilis, tuberculosis
- Post-vaccinal (rabies)
- Systemic autoimmune disease
  - Systemic lupus erythematosus
  - Sjogren's syndrome
  - Behçet disease
  - Antiphospholipid syndrome
- Sarcoidosis
- Multiple sclerosis
- Neuromyelitis optica
- Acute demyelinating encephalomyelitis
- Paraneoplastic syndrome
- Drugs and toxins
  - Tumour necrosis factor-alpha inhibitors
  - Sulphasalazine
  - Chemotherapeutic agents (cisplatin, gemcitabine)
  - Heroin abuse
- Vascular
  - Vasculitis secondary to heroin abuse
- Idiopathic

Clinical Features

- TM symptoms develop rapidly over several hours to several weeks. Approximately 45% of patients worsen maximally within 24 hours. Deficit may progress over several more days to a complete transverse sensorimotor myelopathy.
- Common presenting symptoms of TM include limb weakness, sensory disturbance, bowel and bladder dysfunction.
- Neuropathic pain may occur in the midline (an aching, deep pain) or in a dermatomal distribution (radicular or lancinating pain or a sensation of burning or itching), with the latter pattern providing a clue to the anatomical level of the lesion.
- Almost all patients will develop leg weakness of varying degrees of severity. The arms are involved in a minority of cases and this is dependent upon the level of spinal cord involvement.
- Acutely, limb tone and muscle stretch reflexes maybe diminished and even absent (spinal shock syndrome) leading to possible diagnostic confusion with Guillain–Barre syndrome.
- Sensation is diminished below the level of spinal cord involvement in the majority of patients (sensory level).
- Some experience tingling or numbness in the legs.
- Pain and temperature sensation are diminished in the majority of patients.
- Appreciation of vibration and joint position sense may also be decreased or maybe spared.
- Bladder and bowel sphincter control are disturbed in the majority of patients.
- Demyelination is responsible for the presence of Lhermitte's sign (paraesthesias that radiate down the spine or limbs with neck flexion). It suggests an intrinsic cervical spinal cord lesion, typically affecting the dorsal columns.
- Recovery maybe absent, partial or complete, and generally begins within 1–3 months.

Diagnosis

- The first step is to exclude a mass-occupying lesion that might be compressing the spinal cord. This is important because early surgery to remove the compression may sometimes reverse neurologic injury to the spinal cord.
- Diagnosis requires MRI and CSF analysis.
- MRI typically shows cord swelling and gadolinium-enhancing lesions (single or multiple). Lesions associated with multiple sclerosis usually span less than three vertebral segments. Longitudinally extensive TM occurs in idiopathic TM, neuromyelitis optica, ADEM, cord infarction and myelitis associated with systemic diseases such as systemic lupus erythematosus. MRI also helps exclude other treatable causes of spinal cord dysfunction (e.g. spinal cord compression).

- CSF usually contains monocytes, protein content is slightly increased and IgG index is elevated:
  - IgG index is a measure of intrathecal synthesis of immunoglobulin.
  - Calculated with the use of the formula: (CSF IgG ÷ serum IgG) ÷ (CSF albumin ÷ serum albumin).
  - Normal <0.66.
- Tests for treatable causes of myelitis should include chest X-ray; tuberculin; serologic tests for mycoplasma, Lyme disease and HIV; vitamin B_{12} and folate levels; ESR; antinuclear antibodies; CSF and blood for Venereal Disease Research Laboratory (VDRL) tests; serum NMO-IgG antibody.
- Brain MRI as multiple sclerosis may present with TM.

Diagnostic Criteria

- Bilateral (not necessarily symmetric) sensorimotor and autonomic spinal cord dysfunction
- Clearly defined sensory level
- Progression of clinical deficits to maximum between 4 hours and 21 days after symptom onset
- Demonstration of spinal cord inflammation
  - Cerebrospinal fluid pleocytosis, or
  - Elevated IgG index, or
  - MRI revealing a gadolinium-enhancing cord lesion
- Exclusion of compressive, post-radiation, neoplastic and vascular causes

Treatment

- Despite the lack of randomised controlled studies, administration of high-dose IV corticosteroids should be started as early as possible in all patients. If it fails, plasmapheresis should be tried.
- Treatment of the underlying cause.
- Otherwise, treatment is supportive (see "paraplegia").

Q. How do you differentiate between extradural, intradural extramedullary and intradural intramedullary myelopathies?

Extradural Extramedullary Myelopathy

- Localised pain common and early
- Local deformity
- Root pains common
- Lower motor nerve (LMN) involvement localised to the site of involvement
- Pyramidal signs late
- Bladder involvement late
- Early sacral sensory loss

Intradural Extramedullary Myelopathy

- Root pains less common compared to extradural
- LMN involvement localised
- Bladder involvement rare
- Early onset of pyramidal signs producing spasticity
- Early sacral sensory loss

Intradural Intramedullary Myelopathy

- Root pains uncommon
- LMN involvement spreads over many segments
- Bladder involvement common
- Pyramidal signs late in onset
- Dissociated sensory loss maybe present—e.g. syringomyelia
- May have "sacral sparing" (sacral sensory loss delayed)

Q.   How will you differentiate between conus medullaris lesions and cauda equina lesions?

- Spinal cord terminates at the level of intervertebral disc between the first and second lumbar vertebrae, forming the conus medullaris, below which is the filum terminale and a bundle of nerve roots.
- Cauda equina is formed by nerve roots caudal to the level of spinal cord termination (below L1 vertebral level) which give horsetail-like appearance.
- Conus medullaris is the most distal bulbous part of the spinal cord. It consists of sacral spinal cord segments.
- Cauda equina syndrome refers to a characteristic pattern of neuromuscular and urogenital symptoms resulting from simultaneous compression of multiple lumbosacral nerve roots below the level of conus medullaris. The nerves provide sensory innervation to saddle area, motor innervation to sphincters and parasympathetic innervation to bladder and lower bowel.
- Conus medulllaris is in proximity to the nerve roots and any lesion of this area often results in a combination of upper motor neuron and lower motor neuron symptoms and signs in the dermatomes of the affected segments.

Features	Cauda equina	Conus medullaris
• Onset	Asymmetrical and gradual	Symmetrical and acute
• Dissociated sensory loss	Absent	Present
• Root pain	Common	Rare
• Low backache	Common	Rare
• Fasciculations	Common	Rare
• Bladder and bowel involvement	Early or late (depends on root involvement)	Early
• Muscle tone	Decreased	Increased
• Knee and ankle reflexes	Both absent	Knee present but ankle absent
• Anal reflex	Absent or diminished	Normal
• Perianal (saddle) numbness	Yes (saddle anaesthesia)	No ("perianal" sparing)

Q.   Discuss briefly about neurocutaneous syndromes.

- Neurocutaneous syndromes are genetic disorders that lead to growth of tumours in various parts of the body. Involvement of skin and nervous system is typical of these disorders.

Neurofibromatosis

- Both type 1 and 2 neurofibromatosis have autosomal dominant inheritance.

Neurofibromatosis Type 1 (von Recklinghausen's disease)

Diagnostic Criteria

Two or more of the following:
1. Six or more café au lait spots, greater than 5 mm in diameter in pre-pubertal and over 15 mm in diameter in post-pubertal individuals
2. Two or more neurofibromas of any type or one plexiform neurofibroma
3. Axillary and/or inguinal freckling (Crowe's sign)
4. Optic nerve glioma
5. Two or more Lisch nodules
6. Osseous lesions such as dysplasia of the sphenoid wing, thinning of long bone cortex, with or without pseudoarthrosis
7. First-degree relative (parent, sibling or offspring) with NF type 1 according to above criteria

Neurofibromatosis Type 2

Diagnostic Criteria

One of the following:
1. Bilateral vestibular schwannomas
2. A first-degree relative with NF type 2, and either
   a. A unilateral vestibular schwannoma or
   b. Two of the following: meningioma, posterior subcapsular lens opacity, schwannoma, glioma, neurofibroma or cerebral calcifications
3. Unilateral vestibular schwannoma plus two of following
   a. Meningioma
   b. Schwannoma, glioma, neurofibroma, posterior subcapsular lens opacity or cerebral calcification
4. Multiple meningiomas plus
   a. Unilateral vestibular schwannoma or
   b. Two of schwannoma, glioma, neurofibroma, posterior subcapsular lens opacity

Tuberous Sclerosis

- Autosomal dominant.
- Characterised by formation of hamartomas in multiple organ systems.
- Clinically, characterised by seizures, cutaneous lesions and mental retardation.
- Skin lesions:
  - Adenoma sebaceum—facial angiofibroma.
  - Ash leaf hypopigmentation.
  - Shagreen patch—yellow thickening of skin over lumbosacral region.
  - Calcified subependymal nodules.
- Rhabdomyosarcomas of the myocardium.
- Angiomyolipomas of the kidneys, liver, pancreas and adrenals.
- Increased frequency of ependymomas and astrocytomas.

Sturge–Weber Syndrome

- Sporadic disease.
- Characterised by vascular malformation with capillary venous angiomas that involve the face, choroid of the eye and leptomeninges.
- Facial angioma has a predilection for the distribution of the first division of the trigeminal nerve.
- Angiomatous meningeal malformation.
- Atrophy of the cerebral hemisphere often present.
- Usually unilateral.
- Focal seizures on contralateral side in most patients (80%).
- Mental retardation in more than 50%.
- Glaucoma on the same side as the skin lesions.
- Radiographic hallmark on CT brain is "tramline" or gyriform calcifications usually involving the occipital and parietal lobes.

von Hippel–Lindau Syndrome

- Autosomal dominant.
- Retinal, cerebellar and spinal haemangioblastoma; CNS haemangioblastoma being the most commonly recognised manifestation (in 40% of patients).
- Renal cell carcinoma.
- Phaeochromocytomas.
- Cysts and tumours of kidney, pancreas and liver.

Q. Discuss the aetiology, clinical features, diagnosis and management of lumbago sciatica syndrome.

Q. Discuss the clinical manifestations, investigations and management of intervertebral disc prolapse (IVDP).

- Lumbago is acute low backache.
- Sciatica is the neuralgic pain that starts in the back and radiates along the posterior aspect of lower limb to heel.

Causes

- Combination of lumbago with sciatica is invariably due to acute intervertebral disc protrusion in the lumbar region (L3–L4; L4–L5; L5–S1).
- Other rare causes are the following:
  - Metastasis
  - Tumours
  - Tuberculosis of spine
  - Spinal canal stenosis

Clinical Features of Intervertebral Disc Prolapse (IVDP)

Lumbago

- Lumbago is localised low backache in the midline that increases on movements of spine or straining (like coughing, sneezing, etc.). There is associated paraspinal muscular spasm.
- Pain starts acutely, usually while attempting to lift weight in bent posture. Lumbago may or may not be associated with sciatica.

Sciatica

- Also known as lumbar radicular pain.
- Occurs due to irritation of a spinal root compressed by the protruded disc close to the intervertebral foramen.
- Pain is shooting, burning or shock-like in character. It maybe continuous or brought on by spinal movements and straining.
- Patient prefers to lie down on his sides with flexed lower limbs.
- Syndrome of pain may or may not be associated with symptoms of neurological deficit, which depends on the root involved.

- **L4 root** Weakness of invertors of foot, sensory impairment at L4 dermatome (inner aspect of leg) and depressed knee jerk
- **L5 root** Weakness of extensor hallucis longus with sensory impairment at L5 dermatome (outer aspect of leg and dorsum of foot)
- **S1 root** Weakness of plantar flexors of toes, foot and hamstrings with depressed ankle jerk and sensory impairment at S1 dermatome (outer aspect of foot)

- Positive straight leg raising (SLR) test is present.
- Large disc protrusions may cause bilateral, more extensive neurological deficit (cauda equina syndrome).

Investigations

- Plain radiograph of lumbosacral spine:
  - Loss of lumbar lordosis
  - Scoliosis
  - Reduced intervertebral disc space
  - On most occasions, radiograph is normal
- CT scan shows the protruded disc. MRI is more sensitive and specific.

Treatment

- Conservative management is preferred when no neurological deficit is present.
- Bed rest for 1–3 weeks; however, presently early return to daily activities is encouraged.
- Analgesics and muscle relaxants.
- Surgery is recommended when neurological deficit is present.

Q. Discuss the aetiology, clinical features, investigations and management of syringomyelia.

Q. Give a brief account of dissociated suspended anaesthesia.

- Syringomyelia is a disorder where cavitations (syrinxes) occur within spinal cord along with dilated central canal.
- Syrinxes commonly develop in the lower cervical and high thoracic regions or in the high cervical region where they may extend proximally to the medulla or pons (syringobulbia).
- Many cases are associated with Chiari malformations (usually type I in which there is caudal herniation of the cerebellar tonsils exceeding 5 mm below the foramen magnum).

Causes

- Congenital development (or idiopathic)
- Associated with tumours (intramedullary)
- Post-traumatic
- Arachnoiditis

Clinical Features of Idiopathic Type

- Disorder is chronic.
- Common in females.
- Age of onset is third to fourth decade of life.
- Numbness in upper limbs with frequent burns and injuries that are painless.
- Later, spastic weakness in lower limbs with urinary bladder involvement occurs.

Signs

- Physical findings suggest central cord syndrome or syringomyelic syndrome. They are the following:
  - LMN signs in upper limbs, usually at C_8-T_1 myotomes with wasting of muscles in the neck, shoulders, arms and hands with absent reflexes in the upper limb.
  - Dissociated suspended anaesthesia—There is loss of pain and temperature sensation bilaterally with intact touch and proprioception (dissociated) over dermatomes of upper limbs, and intact sensations above and below (suspended). This is due to lesion at anterior commissure of spinal cord. This disrupts crossing pain and temperature fibres at midline.
  - Pyramidal signs in lower limbs.
- At times, signs to suggest spinothalamic tract involvement maybe seen on one side or bilaterally over trunk and lower limbs.
- Sensory disturbance may extend to neck and face.
- Thoracic kyphoscoliosis is common.

Investigations

- Plain radiograph of cervical spine may show widened cervical spinal canal and associated bony craniovertebral anomalies like basilar invagination, etc.
- Myelogram may show widening of spinal cord (rarely done).
- CT scan shows the widened cord.
- MRI is the most sensitive method. It shows fluid-filled cavitation and dilated central canal. MRI of brain and entire spinal cord should be done.

Treatment

- Surgical removal of obstruction of CSF flow, if any, along with syringo-subarachnoid shunt.

Q. Discuss the clinical manifestations, investigations and management of cervical spondylosis/ spondylitis.

- Spondylitis suggests inflammation of intervertebral joints. However, the term commonly refers to degenerative disorder of cervical spine, where intervertebral disc degenerates with changes in adjacent bones and ligaments, which eventually leads

to formation of protruding bar-like structures at intervertebral areas. They may protrude and compromise spinal canal or intervertebral foramen. Maximum changes occur at C5–C6, C6–C7 and C4–C5 intervertebral disc spaces in that order.

Clinical Features

- Bars or protrusions may just produce localised neck pain or cause neurological problems. Neurological problems present as one or both of the following:
  a. Radiculopathy
  b. Myelopathy

Radiculopathy

- Common roots affected are C5, C6 and C7. It results in root pain with neurological deficit. Radiculopathy is a feature of dorsolateral protrusions. Onset is usually acute or may occasionally be chronic. Neck movements worsen pain.

Root	Muscle	Sensory loss	Reflex
• C5	Biceps, deltoid, spinatus	Upper lateral arm	Biceps
• C6	Brachioradialis	Radial aspect of lower arm extending to thumb	Supinator
• C7	Triceps	Middle finger	Triceps

Myelopathy

- Occurs when protrusions (bars) occur dorsomedially.
- Insidious onset with variable progression.
- Usually painless.
- Acute worsening may follow trauma.
- Pyramidal disturbance with impaired joint position sense (with positive Romberg's sign) is seen in lower limbs.
- Upper limbs get involved later in various combinations of upper and lower motor neuron lesions depending on the level of compression (C4, C5, C6 or C7). Multiple levels maybe evident.
- Bladder gets involved later.

Investigations

- Plain radiograph of cervical spine shows reduced intervertebral spaces with bony protrusions (degenerative changes).
- Myelogram clearly demonstrates the level of lesion (rarely done at present).
- CT scan or MRI can demonstrate the disordered (bony) anatomy and precise level of cord compression.

Treatment

- Conservative management is preferred when no neurological deficit is seen. It includes rest, analgesics, intermittent cervical traction and cervical collar followed by tonic neck exercises.
- Surgery is indicated when neurological deficit is present. Surgical procedures are laminectomy, foraminal decompression and discectomy from anterolateral approach.

Prognosis

- Radiculopathy responds well to treatment.
- Myelopathy has variable prognosis, which may arrest or improve even without treatment.

Q. What are the causes and clinical manifestations of Brown–Sequard syndrome?

- Brown–Sequard syndrome refers to findings seen in hemisection of the spinal cord.
- In disease states it is never seen in its pure form, except maybe in stab injuries.

Other Causes

- Intradural tumours
- Infarction of spinal cord ⎤
- Radiation myelopathy   ⎟ All produce incomplete or additional findings.
- Myelitis

Clinical Manifestations

Features	Ipsilateral	Contralateral
• At level of lesion	• LMN signs (atrophy with depressed jerks) • All modalities of sensations are lost with or without hyperaesthesia	—
• Below level of lesion	• UMN signs (hypertonia, exaggerated DTR and extensor plantar response) • Impaired joint position and vibration sense	• Impaired pain and temperature sense

Strictly unilateral lesions do not produce bladder problems. If lesion is large and extends across midline, bladder involvement is expected

Q. What are the physical signs of posterior column lesion?

Sensations Conveyed by Posterior Column

- Joint position sense
- Vibration sense
- Fine touch
- Cortical sensations (form, shape, weight, location of tactile sensation)

Physical Signs of Posterior Column Lesion

- Sensory ataxia
- Impaired joint position sense
- Positive Romberg's sign
- Impaired stereognosis, tactile localisation and discrimination
- Impaired vibration sense

Romberg's Sign

- Romberg's sign is seen in sensory ataxias.

Method of Eliciting

- Patient is asked to stand with his feet as close as possible (being steady) with eyes open. On closure of eyes he tends to lose his balance if the sign is positive. When it is negative, closure of eyes makes no significant difference in maintaining steadiness.

Physiological Basis

- Necessary sensory information for maintaining equilibrium in upright posture comes from eyes, labyrinths, joints and muscles in lower limbs and trunk. Information is complementary to one another and redundant. In the absence or impairment of one, it is possible for CNS to compensate. In the presence of impaired proprioception visual clues help CNS to maintain equilibrium. When such clues are removed unsteadiness appears.

Q. What are the diseases affecting posterior column? Give the clinical features of any one of them.

Q. Discuss the aetiology, clinical features and management of subacute combined degeneration.

Diseases Affecting Posterior Column

- Subacute combined degeneration
- Tabes dorsalis
- Posteriorly located compressive lesions
- Cervical spondylosis with ligamentum flavum hypertrophy
- Any advanced cord compression
- Transverse myelitis

Subacute Combined Degeneration

- It is a nutritional disorder of CNS due to vitamin B_{12} deficiency, including pernicious anaemia.
- Deficiency of vitamin B_{12} leads to lack of adenosylcobalamin that is required as a cofactor for the conversion of methylmalonyl-CoA to succinyl-CoA. This leads to accumulation of methylmalonyl-CoA, causing a decrease in normal myelin synthesis and incorporation of abnormal fatty acids into neuronal lipids.

- Condition is characterised by demyelination of corticospinal tracts and posterior column. It is usually associated with peripheral neuropathy, optic neuritis and mental changes.

Clinical Features

- Subacute in onset (over weeks).
- Paraesthesia in lower limbs, associated with sensory ataxia.
- Examination shows impaired tactile sensation in glove and stocking distribution.
- Impaired joint position and vibration senses.
- Absent ankle jerks (due to associated peripheral neuropathy) with extensor plantar response and brisk knee jerks.
- Megaloblastic anaemia is usually present, but not necessarily.
- Associated optic neuritis and dementia maybe seen.
- MR imaging of spinal cord shows abnormally increased T2-signal hyperintensity in posterior columns, and occasionally in lateral columns.

Treatment and Prognosis

- Injection hydroxocobalamin or cyanocobalamin 1 mg daily for 5 days followed by 1 mg once in 1–3 months. After improvement injectable preparation maybe changed to oral methylcobalamin.
- Anaemia responds very well to treatment.
- Ataxia and sensory signs improve well if treatment is initiated early.
- Dementia and spasticity often persist.

Q. Discuss the aetiology, clinical manifestations, management and prognosis of motor neuron disease.

Aetiology

- Aetiology is unknown. There is loss of motor neurons and gliosis in motor cortex, motor nuclei of brainstem and anterior horn of spinal cord with degeneration of corticospinal tract in spinal cord.

Classification

Hereditary	Sporadic
• Werdnig–Hoffmann disease [Infantile spinal muscular atrophy (infantile SMA)] • Kugelberg–Welander disease [Adolescent spinal muscular atrophy (adolescent SMA)] • Others	• Amyotrophic lateral sclerosis (most common) • Progressive muscular atrophy (PMA) or spinal muscular atrophy (SMA) • Progressive bulbar palsy • Primary lateral sclerosis (PLS) • Multifocal motor neuropathy with conduction block

Clinical Features

General

- Insidious onset and steadily progressive course.
- Combination of lesions of UMN and/or LMN is characteristic.
- Widespread fasciculations are common. There is no sensory or bladder involvement.
- Average age of onset is sixth decade.
- Four patterns are recognised in early stages that later merge with each other.

Progressive Bulbar Palsy

- Dysarthria, dysphagia and dysphonia.
- Impaired articulation occurs early with low volume of speech.
- Difficulty in swallowing and hoarseness occur later.
- Signs of true (nuclear or bulbar) as well as supranuclear (pseudobulbar) bulbar palsy often coexist.
- Wasting and fasciculations of tongue along with spasticity.
- Jaw jerk is exaggerated.
- Emotional lability with uncontrolled laughter and crying.

Amyotrophic Lateral Sclerosis (ALS)

- Commonest mode of onset.
- "Amyotrophic" means muscle atrophy and "lateral sclerosis" refers to pathologic changes in the spinal cord (and brain stem) that include degeneration of the lateral columns where the corticospinal tracts are located.
- Starts in the limbs in about two-thirds of patients (spinal form); bulbar onset in one-third of patients.
- Bulbar involvement can be UMN (pseudobulbar palsy) or LMN type (bulbar palsy).
  - Bulbar palsy is associated with upper and lower facial weakness and poverty of palatal movement with wasting, weakness and fasciculation of the tongue.
  - Pseudobulbar palsy is characterised by emotional lability (also known as pathological laughing or crying), brisk jaw jerk and dysarthria.
- In the extremities:
  - Generally, LMN signs in upper limbs and UMN signs in lower limbs.
  - Cervical-onset amyotrophic lateral sclerosis presents with upper-limb symptoms, either bilateral or unilateral. Proximal weakness can present as difficulty with tasks associated with shoulder abduction (e.g. hair washing, combing, etc.), and distal weakness produces wasting of small muscles of hands that manifests with impairment of activities requiring pincer grip. Later, wasting and fasciculation spread to proximal arm muscles. In upper limbs, both UMN and LMN signs can occur. Thus, DTR in upper limbs become exaggerated (UMN involvement) in spite of atrophic muscles. Lower limbs would have UMN signs (spasticity of legs, extensor plantar response and exaggerated DTR in lower limbs).
  - Lumbar onset implies degeneration of the anterior-horn cells of the lumbar spinal area and is associated with LMN features in the legs, such as a tendency to trip (foot drop) or difficulty in climbing stairs (proximal weakness).
  - Thoracic onset is generally diagnosed with paraspinal EMG.
- Extraocular movements, sensation and bladder function are typically normal.
- Depression is common in these patients.
- A definite diagnosis of ALS is made by confirming a progressive course of weakness, with both UMN and LMN findings in three out of four anatomically defined regions of the body: Craniobulbar, cervical, thoracic and lumbosacral.

Progressive Muscular Atrophy (PMA) or Spinal Muscular Atrophy (SMA)

- SMA is divided into four types:
  - SMA type I or Werdnig–Hoffman disease, usually presents before 6 months of age. Infants are unable to sit unaided and death often occurs before 2 years without respiratory support.
  - Children with SMA type II become symptomatic before 18 months, can sit but not stand unaided, and survival is variable.
  - SMA type III (also known as Kugelberg–Welander disease) presents in adolescence. Patients can walk or run and survive to adulthood.
  - Type IV SMA denotes adult-onset cases.

Type IV SMA (Adult-Onset SMA)

- Male:female ratio is 5:1.
- Involvement of only LMN.
- Foot drop is the initial manifestation and is usually unilateral, later becomes bilateral and symmetrical.
- Wasting and weakness of hands occur later.
- Deep tendon reflexes diminished or absent.
- Proximal spread of LMN affection in limbs occurs gradually (years later UMN signs appear in limbs).

Primary Lateral Sclerosis (PLS)

- It is a rare form of MND.
- Features are confined to upper motor neurons only.
- There is progressive tetraparesis with terminal pseudobulbar palsy.

Variants of Motor Neuron Disease

- Madras motor neuron disease	- Hemiplegic type of MND
- Monomelic amyotrophy	- Crural ALS
- Wasted leg syndrome	- MND with dementia
- Juvenile MND of north India	- MND with parkinsonism

Madras Motor Neuron Disease

- Age of onset is 20–30 years.
- Male:female ratio is 2:1.
- Accounts for 10% cases of MND in South India.
- Gradual, asymmetrical weakness and wasting of limbs progressing over several years, along with pyramidal involvement, finally producing a picture of ALS.
- Weakness of facial and bulbar muscles (related to lower cranial nerves) present.
- Sensorineural deafness and optic atrophy in many patients.
- Most patients survive for over 30 years after onset.
- Reduced serum citrate and increased serum pyruvate levels.

Monomelic Amyotrophy (Hirayama Disease)

- Age of onset 15–25 years.
- Slowly progressive weakness and wasting confined to one limb, generally upper limb. Lower limbs are usually spared.
- Commonest involvement is of elbow flexors, followed by small muscles of hands.
- Brachioradialis is spared.
- Sensory, bulbar and pyramidal signs are absent.

Course

- Variants are common. Pictures of different categories merge and final picture is of severe bulbar palsy + UMN + LMN signs in all four limbs. Full awareness with normal intellectual abilities is maintained till the end.

Diagnosis

- Exclusion of other diseases (secondary motor neuron disease) is important as many of them are treatable. These are listed in the box.

• Parasagittal tumours	• Hyperthyroidism
• Foramen magnum tumours	• Hyperparathyroidism
• Compressive spinal cord lesions	• Myasthenia
• Syringomyelia	• Subacute combined degeneration
• Polymyositis	• Toxins (lead, mercury, aluminium)
• Chronic inflammatory demyelinating polyneuropathy	• Drugs (phenytoin)
• Multiple motor neuropathy with conduction block	• Radiation
• Paraneoplastic	• Poliomyelitis
• HIV myelopathy	• Multisystem atrophy

- Investigations include spine radiography, EMG, nerve conduction velocity (to document LMN involvement), MRI of spine, thyroid function tests and occasionally lumbar puncture.

Treatment

- No curative medical treatment—walking aids, wheel chair and physiotherapy.
- Others include non-invasive ventilation.
- Symptomatic treatments include use of botulinum toxin to control drooling, gastrostomy to reduce aspiration, baclofen or tizanidine for spasticity and selective serotonin reuptake inhibitors for depression.
- Death occurs from pneumonia or respiratory failure.
- Usual duration of survival in bulbar palsy is about 2 years, ALS 4–5 years and PMA 8–10 years.
- Final state consists of anarthria (severe dysarthria resulting in speechlessness), aphagia (complete inability to swallow) and widespread limb weakness in a person with full consciousness.
- The only drug that has a modest effect on survival is riluzole, a sodium-channel blocker that inhibits glutamate release.

Q. Briefly outline classification, clinical features, investigations, diagnosis and treatment of multiple sclerosis.

- Multiple sclerosis (MS) is an autoimmune disease of white matter that occurs due to interaction of genetic factors with unknown environmental factors. In some cases, deep cerebral cortex and cerebral nuclei maybe involved.

- Most frequently affects young and middle-aged people.
- Characterised by chronic inflammation, demyelination, axonal loss in many cases, with remissions and exacerbations of clinical symptoms and signs.

Classification

- Relapsing-remitting multiple sclerosis (RRMS)—85% cases; symptoms and signs typically evolve over a period of several days, stabilise, and then often improve, spontaneously or in response to corticosteroids, within weeks. Patients are clinically stable between these episodes. Since not all relapses remit completely disability develops over time with the stepwise accumulation of deficits.
- Primary progressive multiple sclerosis (PPMS)—10% cases; characterised by gradual progression of disability without superimposed relapses.
- Secondary progressive multiple sclerosis (SPMS)—characterised by gradual progression of disability with or without superimposed relapses following initial RRMS.
- Progressive relapsing multiple sclerosis (PRMS)—5% cases; characterised by gradual progression of disability from disease onset with relapses later in the course of disease.
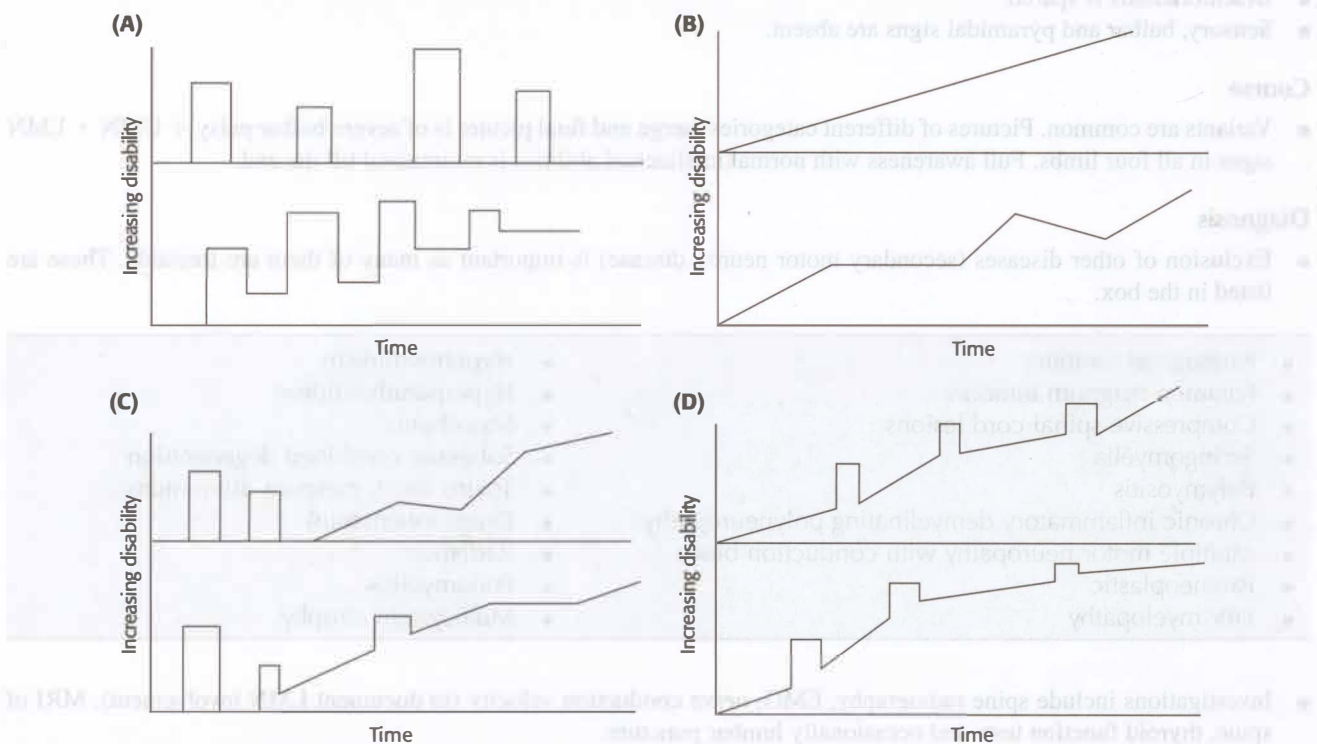
(A) RRMS. There maybe residual deficit from an attack, but the baseline between attacks remains stable until the next attack.
(B) PPMS. There are no acute attacks, but a gradual worsening over time.
(C) SPMS. After an initial course of RRMS the baseline deficit gradually worsens, with or without intervening acute attacks.
(D) PRMS. Starts as primary progressive MS, but has subsequent acute attacks at some point after onset.

Clinical Features

Motor Features

- Predominantly upper motor neuron weakness of muscles (brisk deep tendon reflexes, Babinski's sign, and loss of abdominal reflexes).
- Wasting of muscles of hands and spasticity in advanced cases.

Sensory Features

- Tingling, and numbness common.
- Objective sensory loss including posterior column features. Loss of pain and temperature sensation less common.

Other Features

- Cerebellar signs common. Disequilibrium, truncal or limb ataxia, scanning speech and intention tremor are common in cerebellar findings.
- Optic neuritis usually occurs at the onset of disease.
  - Usually unilateral.
  - Pain with ocular movement is common (unlike ischaemic optic neuritis that is painless).
  - Patients may describe a dimming or bleaching of colour (colour desaturation).
  - Visual acuity may or may not be affected.
  - Visual field loss is often present. Central scotoma is common.
  - Optic disc often appears entirely normal because inflammation is predominately retrobulbar.
  - An afferent pupillary defect is typically present on the swinging flashlight test (Marcus-Gunn pupil). The pupils will be equal in size before testing because of consensual light response. For swinging flashlight test, shining the light on normal pupil causes constriction of both pupils (direct and consensual reflex). The light is then swung to the opposite (affected) pupil. Both the pupils will dilate due to afferent defect.
    - Other ocular features include diplopia and nystagmus. Cranial nerve III palsy and internuclear ophthalmoplegia (usually bilateral) may occur.
    - Pulfrich effect may occur when conduction latencies between the eyes are unequal, resulting in a sense of disorientation in moving traffic.
- Bladder and bowel involvement.
- Uhthoff's phenomenon is worsening of symptoms on exposure to heat (hot water bath) or exercise, and occurs due to conduction block.

Paroxysmal Features

- Trigeminal neuralgia
- Facial weakness
- Vertigo
- Dysarthria
- Epilepsy
- Emotional changes, and delusions
- Lhermitte sign (shooting electric pain in the neck with radiation to the shoulders on flexing the neck and occurs due to posterior column involvement)

Diagnosis

- Age of onset of MS between 10 and 50 years.
- The diagnosis of MS is based on finding clinical evidence of CNS lesions that are disseminated in time and space.
- An acute episode must last for at least 24 hours in the absence of fever or metabolic derangements.
- Dissemination in time means that there is more than one episode of CNS dysfunction. All events occurring within 30 days of an event are considered to be part of a single event.
- Dissemination in space indicates involvement of more than one area of the CNS. Both dissemination in time and space can be diagnosed by performing an MRI if only one episode or one site is obvious on history and examination. Dissemination in space can also be documented by evoked potentials that may indicate an involved area that is otherwise asymptomatic.
- Presence of prominent cortical signs like aphasia, apraxia, recurrent seizures, visual field loss and early dementia, and extrapyramidal signs such as chorea and rigidity generally excludes a diagnosis of MS.

Investigations

- Cerebrospinal fluid: Increased cells (<75/μL), raised protein (<1000 mg/dL) and increased IgG. Electrophoresis of CSF shows oligoclonal bands. CSF analysis is probably most useful for ruling out infectious or neoplastic conditions that mimic MS.
- Visual, auditory and somatosensory evoked potentials show prolongation, and help in diagnosing involvement of clinically silent lesions.
- MRI is very sensitive for detecting lesions that are typically periventricular in location. It can show lesions dispersed both in time (new and old lesions) as well as in space (at different locations). In patients with optic neuritis, gadolinium-enhanced T1 sequences reveal optic nerve enhancement in most patients.

Treatment

Acute Exacerbation

- Methylprednisolone 1 g IV daily for 3 days is the standard therapy. It is followed by oral prednisolone 60 mg for 5 days and then tapered off.

Disease-Modifying Drugs

- These include interferon β-1b, interferon β-1a, mitoxantrone, glatiramer acetate and natalizumab. These are used to reduce disease progression and relapses. Others are fingolimod and teriflutimide.
- Maybe used in RRMS and SPMS varieties.
- Mitoxantrone is the only medication approved for progressive disease.

Symptomatic Treatment

- Spasticity—baclofen (15–18 mg/day), tizanidine (2–8 mg/day), and diazepam (5–10 mg/day)
- Pain—carbamazepine (100–1200 mg/day), gabapentin (300–3600 mg/day), and phenytoin (300–400 mg/day)
- Paroxysmal symptoms—carbamazepine, gabapentin or acetazolamide
- Spastic bladder—anticholinergics like oxybutynin (5 mg TDS), tolterodine (1–2 mg BID) or propantheline (7.5–15 mg QID)

Q. Write a short note on neuromyelitis optica (Devic's disease).

- An idiopathic inflammatory demyelinating disease distinct from multiple sclerosis, which probably has a worse natural history than MS.
- More common in females.
- Optic neuritis maybe unilateral or bilateral. It is almost always acute, usually severe and may or may not be associated with retro-orbital pain. Visual loss is common.
- Neurological dysfunction due to myelitis worsens over several hours to days and involves motor, sensory and sphincter function.
- Fatal autonomic disturbances may occur due to the involvement of autonomic outflow in thoracic myelitis.
- Lower brainstem involvement can occur from contiguous cervical myelitis, and produces nausea, intractable hiccups and respiratory failure. In some cases, hypothalamus and other areas of brain maybe involved. Diencephalic involvement may manifest as hypersomnolence, narcolepsy, syndrome of inappropriate antidiuretic hormone secretion, or menstrual irregularities.
- High frequency of coexisting autoimmune conditions including SLE, Sjögren syndrome, juvenile rheumatoid arthritis, Graves disease, and autoimmune hepatitis,
- MRI of spinal cord helps in diagnosis. The spinal cord lesions are central, contiguous and longitudinally extensive (involving more than three spinal vertebral segments), often involving grey matter and resemble those of complete acute TM. In contrast, in MS, spinal cord involvement is peripheral and restricted to one or two vertebral segmental levels.
- MRI brain abnormalities are present in many cases but are quite distinct from MS lesions. Cerebral lesions are usually linear, as opposed to oval lesions in MS.
- CSF oligoclonal bands are uncommon, whereas a neutrophilic pleocytosis ($\geq$50 cells/mm^3 and $\geq$5 neutrophils/mm^3) occurs commonly during acute attacks.
- One or more autoantibodies, including antinuclear antibody, anti-double-stranded DNA antibody, extractable nuclear antigen, and antithyroid antibodies are commonly present at the time of diagnosis.
- Another autoantibody commonly present in serum is NMO IgG that is directed against water channel aquaporin-4 (aquaporins are membrane water channel proteins important in maintaining fluid homoeostasis in brain).

Course

- Optic neuritis and myelitis can occur simultaneously or in discrete attacks separated by weeks to years. Further, NMO may follow a monophasic or a relapsing course. Patients with a monophasic course have optic neuritis in both eyes and myelitis within a short interval and then have no recurrence.
- Unlike in MS, a secondary progression course is uncommon in NMO.
- For the one-third who have a monophasic course the mean survival is 90% in 5 years. For the other two-thirds, however, who have relapsing course, the survival rate after 5 years is 68%.

Treatment

- Attacks of neuromyelitis optica are more severe, less often steroid responsive, and often lead to significant morbidity and mortality from respiratory failure as a result of cervical myelopathy.

- Intravenous steroids for acute attack.
- Immunosuppressives for prophylaxis (oral steroids + azathioprine or mycophenolate mofetil; rituximab).

Q. Enumerate the common neurological manifestations of vitamin deficiency.

Neurological Manifestations

Vitamin	Deficiency state
• Vitamin A	Night blindness
• Vitamin D	Myopathy of osteomalacia
• Vitamin E	Spinocerebellar syndrome (cerebellar ataxia, hyporeflexia, proprioceptive and vibratory loss, and an extensor plantar response), peripheral neuropathy, visual scotomas, muscle cramps
• Vitamin B complex	
• Thiamin (B_1)	Sensorimotor, distal polyneuropathy (beriberi), Wernicke's encephalopathy, Korsakoff's psychosis
• Riboflavin (B_2)	Polyneuropathy
• Niacin	Dementia (Pellagra includes diarrhoea, dermatitis and dementia), spasticity, myoclonus, peripheral neuropathy
• Pyridoxine (B_6)	Polyneuropathy, convulsions in children (pure sensory neuropathy with B_6 intoxication)
• Cobalamin (B_{12})	Subacute combined degeneration, optic neuritis, dementia, peripheral neuropathy

Q. What is peripheral neuropathy?

Q. What are the commonly encountered causes of polyneuropathies? Discuss the clinical presentation, investigations and management of polyneuropathies.

Q. What are the conditions associated with significant autonomic neuropathies?

Definition

- Any disorder of the nervous system that lies outside the pia mater (peripheral nervous system) is considered peripheral neuropathy.
- Polyneuropathy is a definite clinical syndrome consisting of involvement of all peripheral neurons symmetrically to result in a characteristic clinical picture.
- Mononeuropathy is involvement of one nerve. Most cases are due to compression of a nerve (e.g. carpal tunnel syndrome). Commonly involved nerves are ulnar, median, radial and peroneal nerves. Diabetes mellitus is the most common cause of non-compressive mononeuropathy.
- Mononeuritis multiplex is involvement of multiple peripheral nerves, separated both in anatomic location as well as temporally. Diabetes mellitus is the most common cause.

Types of Peripheral Neuropathy and their Causes

Type	Site	Causes
• Monoradiculopathy	Spinal root	Trauma, tumour, disc protrusion
• Polyradiculopathy	Spinal roots	Arachnoiditis, GB syndrome
• Plexopathy		
• Brachial	Plexus	Trauma, tumours, neuralgia, radiotherapy
• Lumbosacral	Plexus	Tumours, trauma, idiopathic, radiotherapy
• Mononeuropathy*	Single nerve trunk	Trauma, entrapment, leprosy, tumour (neurofibroma), infarction
• Mononeuritis multiplex*	Multiple nerve trunks	Leprosy, trauma, diabetes, PAN, familial pressure sensitive neuropathy
• Polyneuropathy*	Generalised	Separate list follows

*see 408

Focal neuropathy (mononeuropathy)	Mononeuritis multiplex

• Leprosy
• Entrapment
  • Myxoedema
  • Rheumatoid arthritis
  • Amyloidosis
  • Acromegaly
• Trauma
• Ischaemic lesions
  • Diabetes mellitus
  • Vasculitis
• Sarcoidosis
	• Leprosy
	• Diabetes mellitus
	• Vasculitis
	  • Polyarteritis nodosa
	  • Systemic lupus erythematosus
	  • Sjögren's syndrome
	  • Temporal arteritis
	• Sarcoidosis
	• HIV infection
	• Paraneoplastic syndrome
	• Lead poisoning
	• Polycythaemia
	• Cryoglobulinaemia

Classification and Causes of Polyneuropathy

Cause	Nature (clinical)	Nature (pathological)
Acute		
• GB syndrome	Motor	Demyelinating
• Polyarteritis nodosa	Sensory motor	Ischaemic
• Diphtheria	Motor	Demyelinating
• Dapsone	Sensory motor	Mixed
• Acute intermittent porphyria	Motor	Demyelinating
Subacute		
• Nutritional deficiency	Sensory motor	Axonal/mixed
• Toxins		
• Arsenic	Sensory	Axonal/mixed
• Lead	Motor	Demyelinating
• Drugs		
• Chloroquine	Sensory motor	Mixed
• Phenytoin	Sensory motor	Mixed
• Vincristine	Sensory motor	Mixed
• Industrial toxins		
• Carbon tetrachloride	Sensory	Axonal
• Acrylamide	Sensory	Axonal
• Aniline dyes	Sensory	Axonal
Chronic		
• Diabetes	Sensory motor	Mixed
• Carcinoma	Sensory	Axonal
• Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	Sensory motor	Demyelinating
• Hypothyroidism	Sensory	Mixed
• Hereditary	Sensory or motor or mixed	Demyelinating, axonal or mixed

Proximal and Distal Symmetrical Neuropathies

Proximal symmetrical neuropathy (mainly motor)	Distal symmetrical sensorimotor neuropathy

• GB syndrome
• Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
• Diabetes mellitus
• Acute intermittent porphyria
• Diphtheria
• HIV/AIDS
• Hypothyroidism
	• Diabetes mellitus
	• Alcoholism
	• Vitamin B_{12} deficiency
	• Thiamine deficiency
	• Critical illness polyneuropathy
	• Connective tissue diseases (vasculitic)
	  • Rheumatoid arthritis
	  • Polyarteritis nodosa
	  • Systemic lupus erythematosus
	  • Cryoglobulinaemia
	• AIDS
	• Sarcoidosis
	• Toxic neuropathy (acrylamide, carbon disulphide, organophosphorus compounds, arsenic and mercury intoxication)
	• Medications (vincristine, isoniazid, didanosine, dapsone, cisplatin)

Conditions Associated with Significant Autonomic Neuropathies

• GB syndrome • Diabetes	• Acute intermittent porphyria • Certain specific genetically determined neuropathies

Polyneuropathy

- Peripheral nerve fibres can be classified according to size, which correlates with the degree of myelination:
  - Large nerve fibres are heavily myelinated and include A-α fibres, which mediate motor strength, and A-β fibres, which mediate vibratory and touch sensation.
  - Medium-sized fibres, known as A-γ fibres, are also myelinated and carry information to muscle spindles.
  - Small fibres include myelinated A-δ fibres and unmyelinated C fibres, which include somatic (which mediate pain and thermal sensations) and autonomic fibres.
- When the cell body or its axon or myelin is the site of disease, neuron that is longest is affected earlier. Hence, early disturbance occurs at the distal most point in the body.
- Depending on underlying cause and pathology, neuropathies maybe purely motor, predominantly motor, pure sensory or sensorimotor, but most commonly mixed with equal degree of involvement.
- Common causes of small fibre polyneuropathy include diabetes mellitus (burning feet syndrome), alcoholism, vitamin B_{12} deficiency, amyloidosis, pellagra, arsenic intoxication, drug induced (antiretrovirals, cisplatin, isoniazid, nitrofurantoin, vincristine), HIV infection and paraneoplastic.
- Electrophysiologically, it is possible to differentiate neuropathies into demyelinating, axonal or mixed that helps to narrow the diagnostic possibilities.

Clinical Features

- Onset maybe acute (few hours to days), subacute (within 4 weeks) or chronic (over months and years) depending on underlying cause.
- Sensory symptoms may appear in two different ways. Positive sensory symptoms occur when aberrant sensation occurs in the absence of normal stimulation. Negative symptoms occur when adequate stimuli fail to produce a sensory response.

Common features are distal paraesthesias (positive symptoms) initially at toes that ascend up to ankle and leg symmetrically on both sides. It is associated with disturbances of tactile and proprioceptive sensations (negative symptoms).

- Ankle jerk is lost very early (maybe present in axonal neuropathies).
- Later, symptoms appear at fingers and ascend to wrist.
- Depending on nature of pathology, muscular weakness appears initially at toes, ankle, and fingers and wrist in that order. Muscle wasting develops over a period of time. Initial proximal weakness in neuropathies suggests a radicular (nerve roots) involvement or primary muscle involvement (myopathy).
- Fasciculations are rare; when present, suggest distal motor axonal involvement or more likely anterior horn cell disease.
- Autonomic involvement causes orthostatic hypotension, nocturnal diarrhoea, heat intolerance and localised excessive sweating in unaffected areas.
- Other symptoms of autonomic dysfunction include bladder (atonic) dysfunction manifested by difficulty in voiding, sexual impotence, retrograde ejaculation, decreased tearing and pupillary abnormalities.
- Features of small fibre involvement include the following:
  - Burning pain, numbness, tingling in the feet that extends proximally in a stocking-glove distribution
  - Symptoms usually worse at night and often affect sleep.
  - Allodynia (perception of non-painful stimuli as being painful), hyperalgesia (perception of painful stimuli as being more painful than expected) or reduced pinprick and thermal sensation in the affected area.
  - Vibratory sensation can be mildly reduced at the toes.
  - Motor strength, tendon reflexes and proprioception is preserved (because they are functions of large nerve fibres).
  - Autonomic features maybe present.
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is characterised by progressive proximal limb weakness, areflexia, and large fiber sensory loss (distal paresthesias, poor balance, and impaired proprioception). Peak of clinical features occur at least 8 weeks after onset. It is associated with albuminocytologic dissociation in the cerebrospinal fluid (increased albumin with near-normal cells).
- Additional systemic findings are very important as they often give clues to underlying pathology.
  - Signs of nutritional deficiency.
  - Systemic signs of toxicity of drugs and toxins.
  - Presence of malignancy or connective tissue disorder.
  - Presence of skeletal (pes cavus, hammer toes and kyphoscoliosis), visual or auditory involvement in hereditary neuropathies.

Causes of Thickened Nerves

- Leprosy
- Acromegaly
- Amyloidosis
- Neurofibromatosis
- Infiltration of nerves by lymphoma
- Chronic inflammatory demyelinating polyradiculoneuropathy
- Charcot–Marie–Tooth diseases
- Refsum disease

Investigations

- Can be minimised based on thorough clinical evaluation.
- If no clinical clues are forthcoming, following investigations are necessary:

Routing investigations in peripheral neuropathy

- Blood biochemistry
  - Sugar
  - Renal function tests
  - Liver function tests
  - Thyroid function tests
  - Serum immunoglobulins
- Vitamin B_{12} level
- Serology
  - HBsAg
  - Antinuclear antibody factor
  - Rheumatoid factor
- Electrodiagnostic studies
- CSF evaluation
- Nerve biopsy

- Nerve conduction studies define distribution and extent of neuropathy and differentiate between axonal and demyelinating process. In small fibre neuropathy these tests are normal.
- Skin biopsy in suspected small fibre neuropathy.

Treatment

- Curative treatment depends on the underlying cause.
- Corticosteroids, intravenous immunoglobulin, and plasma exchange are useful in CIDP.
- Symptomatic treatment includes the following:
  - Paraesthesias---carbamazepine 300–1200 mg/day, amitriptyline 25–50 mg/day or aspirin 350–1200 mg/day.
  - Weakness—physiotherapy and occupational rehabilitation.
  - Autonomic disturbance-—depends on end organ involvement, e.g. bladder care, managing postural hypotension, etc.

Q. How will you differentiate between axonal and demyelinating neuropathy?

Features	Demyelinating neuropathy	Axonal neuropathy
• Onset	Acute or insidious	Insidious
• Pattern of involvement	Minimal sensory loss	Glove and stock distribution of loss
• Refiexes	Loss of all deep tendon reflexes	Preservation of proximal DTR except ankle reflex
• Recovery pattern	Rapid recovery (over few days to weeks)	Recovery over months to years (if occurs)
• Residual deficit	Less	Common
• Central involvement	Rare	Due to toxic agents
• CSF protein	Raised	Normal
• Nerve conduction	Very slow	Normal or slightly slow

Q. Write a brief note on Guillain–Barre syndrome (GB syndrome), post-infective polyneuropathy, acute inflammatory polyneuropathy or acute inflammatory demyelinating polyradiculoneuropathy (AIDP).

- GB syndrome (GBS) is the commonest acute inflammatory demyelinating polyneuropathy that is presumed to be autoimmune in nature.
- It affects people at any age.
- It usually follows viral infection, rarely after surgery or immunisation.

Pathogenesis

- Exact pathogenesis not known.
- GB syndrome is a monophasic immunologically mediated inflammatory disorder of peripheral nerves. Multifocal demyelination with inflammation results in conduction block. Severe forms show secondary axonal degeneration.
- GB syndrome commonly follows an infection. Antiganglioside antibodies are seen in at least one-third of GBS patients. These antibodies appear to cross-react with antigens in the lipopolysaccharides of some antecedent infective agents. These antibodies act against gangliosides, such as GM1, distributed throughout the myelin in the peripheral nervous system.
- Both cellular and humoral immune mechanisms probably play a role in its development.
- Since inflammation is important in its pathogenesis, GB syndrome is also known as acute inflammatory demyelinating polyneuropathy (AIDP).

Clinical Features

- It is an acute disorder.
- It usually progresses for a few days and rarely up to 1 month.
- It is a predominant motor neuropathy.
- Sensory findings are minimum and consist of distal paraesthesias with mildly disturbed joint position sense.

- Motor paralysis is more striking and is symmetrical, involving proximal muscles more than distal. It begins in the legs, progressing over several days to involve arms, face and eyes (ascending paralysis).
- Reflexes are absent.
- 50% show bifacial weakness.
- Some show bulbar muscular weakness.
- Respiratory paralysis occurs in a few.
- Autonomic disturbances occur in a few, resulting in sudden fluctuations in BP and heart rate.
- Bladder involvement is rare, and even when seen is mild and hardly lasts longer than 1 week.
- Clear sensory level and marked bladder involvement are against the diagnosis of GB syndrome.
- Similarly, extensor plantar response is extremely rare.

Miller Fisher Syndrome

- It is a variant of GB syndrome and is characterised by areflexia, ataxia and ophthalmoplegia without significant limb weakness.
- Often preceded by *Campylobacter jejuni* infection (usually producing diarrhoea).

Other Variants

- Acute motor axonal neuropathy.
  - Progresses more rapidly and has an earlier peak than demyelinating GBS
  - Tendon reflexes are relatively preserved or even exaggerated
  - Autonomic dysfunction is rare
- Acute motor and sensory axonal neuropathy.

Course

- Muscle weakness gradually progresses over 1–3 weeks and then plateaus over next several days to weeks before gradual recovery. On recovery, nearly 15% patients do not have any deficit while minor deficit and major deficits occur in nearly 70% and 5–10% cases, respectively.

Investigations

- CSF becomes abnormal after 1 week of illness and shows raised proteins (> 45 mg/dL), normal sugar and cell count (generally <10/mm³; rarely cell count may go up to 50 cells/mm³, but never above that). This is known as albuminocytological dissociation.
- Nerve conduction velocity studies show slowing of velocities (demyelination pattern).
- Acute intermittent porphyria, post-diphtheritic neuritis and drug-induced acute polyneuropathies will need to be ruled out.

Treatment

- Immediate management of a patient with GB syndrome consists of maintenance of airway, breathing and circulation. Ventilate if patient develops respiratory failure.
- Monitor pulse, BP and cardiac activity using a cardiac monitor as these patients have autonomic instability.
- Steroids are of little value in these patients.
- Plasmapheresis and intravenous immunoglobulin (0.4 g/kg/day for 5 days or 2 g/day for 2 days) have been shown to accelerate recovery.

Q. Discuss the clinical features, investigations and management of myasthenia gravis.

Q. Briefly describe edrophonium test (Tensilon test).

- Myasthenia gravis (MG) is an autoimmune disorder where antibodies are produced against acetylcholine receptors located at motor end plates in myoneural junctions.
- Antibodies are produced by B lymphocytes that are defectively regulated by T lymphocytes. T lymphocyte tolerance to self-antigens is established in the thymus, but in MG this tolerance is lost that results in production of autoantibodies against acetylcholine receptors.
- Thymic hyperplasia is observed in about 65% of MG patients, and thymomas are present in about 10% of MG patients.

Clinical Features

- Age of onset is 15–50 years.
- Females are more affected than males.
- Remissions and relapses are seen during the early course of illness.
- Characteristic feature is easy fatiguability associated with paresis of muscles.
- Repeated contractions worsen the weakness.
- Rest improves the muscular strength.
- Reflexes and sensations are normal.
- Diurnal variation is present.
- Ocular muscles are most commonly affected resulting in ptosis and diplopia. Pupils are not involved.
- Involvement of bulbar muscles results in dysphagia, nasal regurgitation and difficulty in speaking (nasal voice).
- Limb muscle involvement is of proximal group resulting in difficulty in raising the arm above shoulder, and problems in getting up from squatting or sitting positions.
- Involvement of respiratory muscles results in myasthenic crisis and can cause death.
- MG is termed ocular MG when weakness is exclusive to the eyelids and extraocular muscles, and generalised MG when weakness extends beyond these ocular muscles.

Exacerbation of Weakness

- Patients being treated with anticholinesterase agents may present with exacerbation of weakness due to (i) myasthenic crisis or (ii) cholinergic crisis. Other causes of acute respiratory failure due to neuromuscular weakness include snake bite, botulism, organophosphate poisoning, GB syndrome and polymyositis.
    - Myasthenic crisis occurs in patients with MG who are either not on any treatment or are being under-treated due to low dosages or development of drug resistance. Other precipitating factors include exertion, extremes of temperature, infections, surgery, trauma and use of other drugs that can increase myasthenic weakness (see below). By definition, myasthenic crisis is characterised by severe weakness of the bulbar (innervated by cranial nerves) and/or respiratory muscles, enough to cause inability to maintain adequate ventilation, causing respiratory failure that requires artificial airway or ventilatory support.
    - Cholinergic crisis occurs as a result of relative overdose of anticholinesterase drugs. Patients present with muscarinic features (excessive salivation, lacrimation, miosis, abdominal pain, diarrhoea, increased bronchial secretions and urinary incontinence) along with respiratory insufficiency. However, it maybe difficult to differentiate this condition from myasthenic crisis on clinical grounds alone.

Investigations

Tensilon Test (Edrophonium Test)

- Edrophonium is a rapidly acting acetylcholinesterase inhibitor. It has a short duration of action and reverses the muscular weakness dramatically in myasthenia. In adults, a 2-mg injection is given as a test dose (to check for tolerance) followed by another 8 mg that results in dramatic improvement in ptosis, diplopia, nasal voice, etc. within 30 seconds and persists up to 1–2 minutes. Positive test is highly suggestive of MG. Borderline or mild improvement may occur in other neuromuscular disorders. Side effects like abdominal cramps can be relieved by atropine.

Others

- Chest radiography and CT scan for thymic enlargement.
- Thyroid function tests (10% may have associated hyperthyroidism).
- Acetylcholine receptor antibody levels (present in >90% patients with generalised myasthenia).
- Anti-muscle-specific protein (tyrosine) kinase (anti-MuSK) antibodies in many patients who are negative for ACh-receptor antibodies.
- Patients with MuSK-antibody associated MG are usually younger women who present with predominant facial, bulbar and respiratory weakness, lingual atrophy and relatively mild limb weakness.
- Electrodiagnostic studies (nerveconduction testing, repetitive nerve stimulation, exercise testing and in certain instances single-fibre EMG).
- Icetest: In a patient with ptosis a small cube of ice is placed over the eyelid for about 2 minutes. Improvement of the ptosis after this procedure suggests a disorder of neuromuscular transmission.

Management

- Anticholinesterases are effective in providing symptomatic relief. Neostigmine (15 mg) 1–2 tablets, three to six times a day or pyridostigmine 60–120 mg three to six times a day maybe used. Dosage is titrated to the need of the patient. Cholinergic systemic side effects like abdominal cramps and increased salivation are managed with propantheline 15 mg 2–3 times a day. Pyridostigmine is generally better tolerated than neostigmine due to fewer gastrointestinal side effects. Excessive dosage of anticholinesterase can result in cholinergic muscular weakness associated with excessive sweating, salivation, lacrimation, diarrhoea and small pupils. It can be differentiated from myasthenic weakness by edrophonium test. Treatment response with anticholinesterases is much less favourable in anti-MuSK MG, with a significantly increased risk of myasthenic crisis.
- Corticosteroids are useful in induction and maintenance of remission. However, in about 15% patients corticosteroids may worsen symptoms transiently during initial periods of treatment and may precipitate myasthenic crisis.
- Thymectomy can induce remission when the disease is generalised and has not been chronic. It is also recommended in patients with thymoma. Thymectomy may or may not reduce requirement of steroids.
- Immunosuppression with azathioprine, cyclophosphamide, cyclosporine, tacrolimus or mycophenolate mofetil is recommended when the dosage of steroid requirement is too high to maintain remission. Rituximab has also been used in refractory cases.
- Plasma exchange and intravenous immunoglobulin are useful for inducing a short-term remission like prior to surgery or during myasthenic crisis.
- Supportive measures like ventilatory assistance and nasogastric tube feeding maybe required in some cases.

Drugs that may Aggravate Myasthenia Gravis

- Antibiotics—aminoglycosides (most important), polymyxins, colistin, tetracyclines, fluoroquinolones, macrolides, ritonavir
- Cardiovascular drugs—lidocaine, β-blockers, calcium channel blockers, quinidine, procainamide
- Others—chloroquine, penicillamine, interferons, statins, iodinated contrast agents, lithium, carbamazepine, phenytoin, muscle relaxants, curare-like neuromuscular blockers, magnesium

Prognosis

- Prognosis is variable. Deaths are common if crisis occurs in first 2–3 years. Deaths rarely occur after 5–7 years of illness.

Q. Explain muscular dystrophies or hereditary myopathies.

- Group of hereditary disorders characterised by progressive muscle wasting and weakness with histopathological features of "dystrophic" muscle (variation in muscle fibre size, muscle fibre degeneration and regeneration, and replacement of muscle by fibrosis and fat).

Classification

- **X-linked muscular dystrophies**
  - Duchenne muscular dystrophy
  - Becker muscular dystrophy
  - Emery–Dreifuss muscular dystrophy
- **Autosomal muscular dystrophies (can be dominant or recessive)**
  - Limb-girdle muscular dystrophy
  - Others

- **Autosomal dominant muscular dystrophies**
  - Facioscapulohumeral muscular dystrophy
  - Ocular muscular dystrophy
  - Oculopharyngeal muscular dystrophy
  - Myotonic dystrophy
- **Sporadic**
  - Congenital muscular dystrophy

Duchenne Muscular Dystrophy

- X-linked recessive disorder is caused by absence of dystrophin due to mutation of Duchenne muscular dystrophy (DMD) (also known as dystrophin) gene.
- Onset between 3 and 5 years.
- Proximal muscles of lower limbs are affected first followed by proximal muscles of upper limbs. Boys fall frequently.
- On getting up from the floor, patient uses his hands to climb up himself (Gower's sign).
- Later, neck muscles, extraocular muscles, diaphragm and facial muscles involved.

- Patient is bed-ridden by the age of 10 years.
- Pseudohypertrophy of calf muscles and occasionally deltoid muscles.
- Other features include contractures, macroglossia, absence of incisor teeth, mental retardation, skeletal atrophy and cardiac involvement (tachycardia, tall R-waves in right precordial leads, deep Q-waves in limb leads and left precordial leads).
- Serum creatine kinase elevated to at least 20 times the normal.
- EMG shows myopathic pattern (small, short-duration, and polyphasic muscle action potentials).
- Muscle biopsy shows muscle fibres of varying size as well as small groups of necrosis and regenerating fibres. It also shows deficiency of dystrophin (a protein present on inner surface of sarcolemma) by Western blot test.
- Treatment with prednisolone may slow progression for up to 3 years. Others include physiotherapy, management of respiratory and cardiac complications and maintenance of nutrition.

Becker Muscular Dystrophy

- X-linked recessive disorder resulting from partial dystrophin deficiency.
- Onset between 5 and 25 years.
- Pelvic and pectoral muscles predominantly involved.
- Patient unable to walk after about 25 years of onset.
- Significant facial weakness is not common.
- Associated features include cardiac involvement, contractures and hypertrophy of muscles.
- Serum CK is raised.
- EMG shows myopathic pattern.

Myotonic Dystrophy

- Type 1 more common than type 2.
- Autosomal dominant.
- Onset during second decade of life.
- Typical "hatchet-faced" appearance due to atrophy and weakness of temporalis, masseter and facial muscles.
- Neck flexors, sternocleidomastoid and distal limb muscles affected early.
- Dysarthria, nasal voice and swallowing difficulties due to palatal, pharyngeal and tongue involvement.
- Proximal muscles remain strong.
- Myotonia:
  - Percussion of thenal muscles or tongue produces contraction without immediate relaxation.
  - Slow relaxation of hand grip after a forced voluntary closure.
- Frontal baldness.
- Cardiac conduction defects; may produce sudden death.
- Mitral valve prolapse.
- Others include cataract, gonadal atrophy, insulin resistance and intellectual impairment.
- Serum CK normal or mildly elevated.
- EMG shows evidence of myotonia.
- Myotonia usually requires no treatment. If it is severe, phenytoin or mexiletine maybe used.
- Cardiac pacemaker, if cardiac conduction defects produce symptoms.

Q. Differential diagnosis of wasting of small muscles of hand.

- Intrinsic muscles of hand are supplied by C8 and T1 myotomes through median and ulnar nerves.

Causes

Site	Causes
• Spinal cord lesions	Motor neuron disease, syringomyelia, intramedullary tumours, intradural tumours (rare)
• Plexus lesions	C8-T1 root lesions with Horner's syndrome (e.g. trauma, Pancoast's tumour), lower trunk and medial cord lesions (e.g. trauma, metastasis, thoracic outlet syndrome)
• Median nerve lesions	Trauma, carpal tunnel syndrome
• Ulnar nerve lesions	Trauma, leprosy, entrapment at ulnar groove or Guyon's tunnel
• Polyneuropathy	Causes—refer before

Q. Outline the causes of coma. How do you proceed to investigate and manage a case of coma?

Q. Write a short note on Glasgow Coma Scale.

- Consciousness is a state of awareness of the self and the environment.
- Coma is a state where consciousness (wakeful state) is altered severely and is due to depressed brain function. It is defined as a state of altered consciousness from which a person cannot be aroused easily. In contrast, the term confusion indicates lack of clarity and coherent thought, perception, understanding or action. Stupor is defined as disturbed consciousness from which the patient can be aroused by vigorous external stimuli.
- Altered mental status is a continuum and includes any state where the level of consciousness is altered.
- Consciousness is maintained by active cerebral cortex under the influence of ascending reticular activating system, originating from upper brain stem (pons and midbrain) through thalamus radiating diffusely to entire cortex.
- It follows then unconsciousness maybe brought on by functional or structural disturbances of either one or both of the following:
  - Large areas of cerebral cortex (usually both hemispheres).
  - Upper brain stem structures.
- Causes of coma include primary neurological disorders, various systemic disorders and toxins that can impair brain function.

Causes of Coma—Aetiological

Primary neurological disorders	Systemic disorders causing coma
Cerebral hemispherical lesions	**Metabolic encephalopathies**
- Brain tumours	- Hypoglycaemia
- Abscess	- Hyponatraemia
- Cerebral infarcts (large)	- Hyperglycaemia with or without ketosis
- Cerebral haemorrhage	- Anoxia
- SAH	- Hypercapnia
- Subdural haematoma	- Hyperpyrexia
- Hydrocephalus	- Hypo or hyperosmolar states
	- Hepatic and uraemic encephalopathy
Brainstem lesions	- Severe peripheral circulatory failure
- Infarct	
- Haemorrhage	**Miscellaneous**
- Posterior fossa mass lesions	- Toxic encephalopathies secondary to systemic
- Wernicke's encephalopathy	infections
	- Hypertensive encephalopathy
Combination of both (entire brain)	- Poisoning
- Trauma	
- Meningitis, encephalitis	
- Anoxia (post-cardiac arrest)	
- Severe shock states	
- Postictal state following a generalised fit	
- Cerebral depressant drugs (sedatives/hypnotics)	
- Raised ICP due to brain oedema from any cause, e.g. Reye's syndrome	

Evaluation of Severity of Coma

Glasgow Coma Score

Eye opening (E)	Score	Verbal response (V)	Score
- Spontaneous	4	- Oriented	5
- To speech	3	- Confused conversation	4
- To pain	2	- Inappropriate words	3
- None	1	- Incomprehensible sounds	2
		- None	1

Best motor response (M)		Coma score	E + M + V
• Obeys	6	• Fully conscious	15
• Localises	5	• Deeply comatose	3
• Withdraws	4		
• Abnormal flexion	3		
• Abnormal extension	2		
• None	1		

Approach to Problem of Coma

- The first step is to the CABDE (Circulation, Airway, Breathing, Disability and Exposure). Make sure that there is no immediate danger to life by ensuring CAB (Circulation, Airway with cervical spine control, Breathing). Disability is assessed by abbreviated coma scale (AVPU – Alert, responds to Verbal commands, responds to Pain, and Unconscious). The patient should be exposed completely for detailed examination taking care not to expose the patient to extremes of temperature.
- Attach a cardiac monitor and pulse oximeter and administer oxygen. Establish an intravenous access and withdraw blood for various investigations including sugar, urea and electrolytes.
- After initial stabilisation, obtain a brief history from all the relatives and friends. Ask about the details of what happened, any trauma, use of medications, exposure to alcohol, history of seizures, diabetes, hypertension, cirrhosis, previous neurological diseases and associated symptoms like headache.
- History of mode of onset and evolution (or progression) gives clue to underlying mechanism.

Causes of Coma Based on Rapidity of Evolution

Abrupt (within seconds and minutes)
- Cerebral haemorrhage
- SAH
- Massive cerebral infarct
- Cardiac arrest
- Epileptic fit
- Trauma

Acute (within a few hours)
- Cerebral infarct or haemorrhage
- Acute poisoning—alcohol, drugs
- Hypoglycaemia in diabetics due to overdosage of insulin or oral hypoglycaemics

Subacute (within several hours and a few days)
- Metabolic encephalopathies
- Brain tumours, other mass lesions
- Encephalitis and meningitis
- Toxic encephalopathies secondary to severe systemic infections

Physical Examination

- Physical examination of a comatose patient should include the following:
  - Level and severity of coma.
  - Lateralised focal deficits (hemiparesis, facial weakness, etc.).
  - Pupillary size and response.
  - Pattern of motor response and respiration.
  - Oculocephalic reflex (doll's eye phenomenon)—only after excluding cervical spine injury.
  - Oculovestibular reflex.
  - Complete systemic examination.
  - Exclude a serious systemic or traumatic condition causing altered level of consciousness.
- Presence of lateralised focal deficits suggests a primary neurological disorder. However, patients with hypoglycaemia and hepatic failure can show focal deficits.

- Altered brainstem reflexes suggest a primary or secondary brain stem involvement.
- Features of metabolic encephalopathies are small reactive pupils, normal oculocephalic reflex and flaccid limbs.
- Respiratory pattern depends on the underlying metabolic problem:
  - Deep and rapid breathing with acidosis in diabetic ketoacidosis and uraemic encephalopathy.
  - Cyanosis with deep and rapid breathing in respiratory failure with hypercarbia.
  - Pale person with rapid breathing in shock states.
  - Respiratory alkalosis without hypoxia in hepatic encephalopathy.
  - Sluggish, slow breathing in barbiturate or other sedative drug poisoning.

Investigations

- Following accurate clinical evaluation, most useful investigations include CT scan (CT), CSF evaluation (CSF), metabolic parameters check (blood biochemistry or BB) and toxicology screening (TS).

Differential Diagnosis

- Coma vigil (vegetative state): Patient is comatose with complete lack of awareness of self or environment, but the eyelids are open giving the appearance of being awake. Patients maintain sleep–wake cycles with full or partial hypothalamic and brainstem autonomic functions. They can open their eyes or have random limb movements but there is no response to commands.
- Minimally conscious state: A condition in which patient appears not only to be wakeful (like vegetative state patients) but also exhibits inconsistent (fluctuating) signs of awareness (unlike patients with vegetative state). The latter includes non-reflexive response to sensory stimulation, awareness of the self or the environment, or language comprehension or expression.
- Akinetic mutism: Akinetic mutism refers to a state in which the patient, although awake, remains entirely silent and motionless. The patient has sleep/wake cycles and can maintain vital functions, but does nothing voluntarily. This condition is often due to bilateral frontal lobe lesions, hydrocephalus and a mass in the region of third ventricle.
- Locked-in-state: The patient is aware and awake. However, due to severe impairment of motor function preventing communication, coma can be mistakenly diagnosed in these patients. This syndrome is due to extensive transverse pontine and midbrain lesions. Their only form of communication maybe through vertical eye movements and blinking.
- Conversion reaction: Patients with conversion reaction (pseudocoma) have normal pupils, corneal reflexes and plantar reflexes. They may keep their eyes firmly shut and resist the opening of the eye by examiners. The eyes roll up when the lids are raised. Roving eye movements cannot be imitated and their presence indicates true coma. The presence of nystagmus during cold caloric testing suggests that coma is either feigned or hysterical.

Approach to Diagnosis of Coma Based on Combined Clinical and Laboratory Data

Normal brainstem reflexes, no lateralising signs

CT abnormal	CT normal
• Hydrocephalus	• Drug induced (TS)
• Bilateral subdural haematoma	• Metabolic encephalopathy (BB)
• Diffuse cerebral contusion or oedema	• Shock, hypertensive encephalopathy
• SAH	• Meningitis, encephalitis (CSF)
• Brainstem haemorrhage	• Reye's syndrome (BB)
• Cerebellar haemorrhage	• Brain-stem infarction
• Cerebellar infarct	• Drug overdosage (TS)
• Posterior fossa mass lesion	• Trauma, brain death
• Large cerebral mass lesion with transtentorial herniation	

Normal brainstem reflexes with lateralising signs

CT abnormal	CT normal
• Cerebral haemorrhage or infarct	• Early cerebral infarct
• Viral encephalitis	• Metabolic encephalopathy with fleeting focal signs (BB)
• Subdural haematoma, tumours, abscess	• Epileptic fit in post-ictal state
• Stroke with metabolic encephalopathy (BB)	

TS—Toxicology screening
BB—Blood biochemistry
CSF—CSF evaluation

Treatment

- Maintain circulation, airway and breathing.
- Diagnose underlying cause at the earliest.
- Adopt appropriate specific treatment at the earliest.
- If patient is a diabetic, administer hypertonic glucose, without waiting for reports. However, it is best to get a bedside estimation of blood glucose and administer dextrose only if the blood glucose is below 100 mg/dL.
- If patient is an alcoholic, administer glucose and vitamin B_1 100 mg intravenously, without waiting for reports.

Care of Unconscious Patient

- Maintain airway and clear off secretions—by frequent assisted clearance.
- Posture of the patient—prone or lateral position prevents aspiration of gastric contents.
- Nasogastric tube—to keep the stomach empty or to feed, depending on underlying situation.
- Bladder care—continuous indwelling catheter or clean intermittent catheterisation.
- Skin care—change of posture once in 2–3 hours, and skin should be kept clean and dry to prevent bed sores.
- Have a secure IV line.

Q. Write a short note on brain death.

- Defined as the irreversible loss of all functions of the brain, including the brainstem.
- Occurs when ICP exceeds CPP, resulting in cessation of CBF and oxygen delivery.
- Concept of brain death is important as: (i) it allows withdrawal of costly life-saving equipments and drugs, and (ii) family can be offered opportunity for organ donation.
- Diagnosis of brain death is primarily clinical. No other tests are required if complete clinical examination including independent brain death determinations by two licensed physicians is conclusive.

Pre-requisites for Proceeding with Clinical Examination to Determine Brain Death

- Clinical or neuroimaging evidence of an acute CNS catastrophe that is compatible with the diagnosis of brain death. A normal CT scan should raise doubt as to the diagnosis of brain death and lead to further imaging studies
- Exclusion of complicating medical conditions that may confound clinical assessment such as severe electrolyte, acid–base or endocrine disorders, and refractory shock (systolic BP <90 mmHg)
- Absence of drug intoxication, poisoning, sedative or neuromuscular blocking agents
- Absence of severe hypothermia (core temperature <32°C). This is because pupillary light reflex is lost at core temperatures of 28–32°C, brainstem reflexes disappear when core temperature drops below 28°C. A core body temperature of >36°C is recommended before proceeding to CNS examination
- Systolic pressure >100 mmHg

Clinical Neurological Examination

- Three essential findings in brain death are coma, absence of brainstem reflexes and apnoea. Therefore, a comprehensive clinical neurologic examination is required before declaring a patient brain dead.
- Coma is defined as no cerebral motor response to pain in all extremities (nail-bed pressure and supraorbital pressure).
- Absence of brain-stem reflexes:
  - Pupils—round or oval pupils measuring 4 to 9 mm with no response to bright light.
  - Ocular movement—no oculocephalic movements on rapid turning of the head (performed only when no fracture or instability of cervical spine is present); no deviation of eyes to cold caloric stimulation, i.e. absent oculovestibular reflex (irrigate each ear with ice water after the head has been tilted 30° to check for eye deviation).
  - Facial sensation and facial motor response—no corneal reflex, no jaw reflex, no grimacing to deep pressure on nail bed, supraorbital ridge or temporomandibular joint.
  - Pharyngeal and tracheal reflexes—no response to stimulation of posterior pharynx with a tongue blade, no cough response to bronchial suctioning.
- Apnoea test:
  - Before performing apnoea test following conditions should be met:
    - Core temperature 36.5°C
    - Euvolaemia

- Normal PCO_2
- Normal PO_2
- Apnoea test is conducted as follows:
  - Connect a pulse oximeter and disconnect the ventilator.
  - Deliver 100% O_2 at 6 L/minute into trachea by placing a cannula at the level of carina.
  - Observe closely for any respiratory movements.
  - Measure arterial PO_2, PCO_2 and pH after approximately 8 minutes and reconnect the ventilator.
  - If respiratory movements are absent and arterial $PCO_2 \geq 60$ mmHg, apnoea test result is positive (i.e. it supports the diagnosis of brain death).
  - If respiratory movements are observed, apnoea test result is negative.

Confirmatory Laboratory Tests

- A confirmatory test is not mandatory, but is desirable in patients in whom specific components of clinical testing cannot be reliably performed.
  - Conventional angiography showing absence of intracerebral filling at the level of carotid bifurcation or circle of Willis.
  - Electroencephalography (EEG) showing absence of electrical activity during at least 30 minutes of recording.
  - Transcranial Doppler ultrasonography showing small systolic peaks in early systole without diastolic flow, indicating very high vascular resistance associated with greatly increased ICP.
  - Technetium-99m CBF scan showing absence of uptake of isotope in brain parenchyma.
  - Somatosensory evoked potentials showing absence of response with median nerve stimulation on both sides.

Clinical Observations Compatible with Diagnosis of Brain Death

- While observing a patient, a few findings maybe seen that should not be misinterpreted as evidence for brainstem function. These are:
  - Spontaneous limb movements other than pathologic flexion or extension response.
  - Respiratory-like movements (shoulder elevation and adduction, back arching, and intercostals expansion without significant tidal volumes).
  - Sweating.
  - Tachycardia.
  - Normal BP without pharmacologic support.
  - Sudden increases in BP.
  - Absence of diabetes insipidus.
  - Presence of deep tendon reflexes or superficial abdominal reflexes.
  - Presence of extensor plantar reflex.
- Common physiological derangements after brain death:
  - Hypothermia.
  - Hypotension.
  - Cardiac arrhythmias.
  - Diabetes insipidus.
  - Disseminated intravascular coagulation.
  - Pulmonary oedema.

Chapter 6

Diseases of the Liver and Biliary System

Q. Enumerate important functions of liver.

- Carbohydrate metabolism including gluconeogenesis, glycogenolysis and glycogenesis.
- Protein metabolism.
- Lipid metabolism.
- Bilirubin metabolism.
- Bile acid formation and secretion.
- Vitamin and mineral metabolism.
- Hormone metabolism.
- Drug and alcohol metabolism.
- Cholesterol metabolism.
- Synthesis of plasma proteins including clotting factors.

Q. Discuss various liver function tests and their significance in jaundice.

Bilirubin in the Blood

- Normal serum bilirubin level is 0.3–1.0 mg/dL.
- Hyperbilirubinaemia may be of conjugated or unconjugated type.
  - Unconjugated hyperbilirubinaemia is characterised by a serum level less than 6 mg/dL and absence of bilirubinuria. The other tests of liver function are normal. Examples are haemolytic diseases, ineffective erythropoiesis and Gilbert's syndrome.
  - Conjugated hyperbilirubinaemia is characterised by higher levels of bilirubin and bilirubinuria. The other tests of liver function are often abnormal. Examples are parenchymal liver diseases and biliary tract obstructions.
  - Fluctuating hyperbilirubinaemia is seen in gallstones, carcinoma of ampulla of Vater, chronic hepatitis, haemolytic anaemias and Gilbert's syndrome.

Bilirubin in the Urine

- Normally bilirubin cannot be detected in urine.
- In unconjugated hyperbilirubinaemia there will be no bilirubin in the urine. Thus, absence of bilirubin in the urine in a jaundiced patient points to unconjugated hyperbilirubinaemia.
- In conjugated hyperbilirubinaemia urine contains bilirubin. Thus, bilirubinuria in a jaundiced patient points to conjugated hyperbilirubinaemia (hepatobiliary disease).

Urine Urobilinogen

- Urinary urobilinogen is detected by Ehrlich's aldehyde test. One millilitre of fresh urine is mixed with 1 mL of Ehrlich's aldehyde reagent. After 1.5 minutes, 2 mL of saturated aqueous sodium acetate is added and mixed, followed by 2 mL of a 3:1 mixture of amyl alcohol and benzyl alcohol. Contents are gently shaken for 1 minute. A red colour of the upper layers indicates urobilinogen. Normally, there is a diurnal variation, being more in the afternoon.
- No urobilinogen in urine in case of obstructive jaundice (bilirubinuria present).
- Increased urobilinogen in urine in viral hepatitis, cirrhosis, malignancy and heart failure (bilirubinuria present).
- Markedly increased urobilinogen in urine in case of haemolytic diseases (no bilirubinuria).

Enzymes

(A) Aminotransferases

- Aspartate aminotransferase (AST, SGOT) and alanine aminotransferase (ALT, SGPT).
  - Normal value 5–40 IU/L.
  - Aminotransferase levels are useful to differentiate between hepatocellular jaundice and obstructive jaundice.
- Alanine aminotransferase (ALT):
  - Concentration of ALT is much higher in the liver than in other tissues (e.g. kidney, heart muscle). Hence, a raised ALT is a very sensitive index of hepatic damage.
    - 100–500 times rise occurs in paracetamol-induced liver damage.
    - 10–100 times rise occurs in:
      - Viral hepatitis (increase in ALT associated with hepatitis C infection tends to be more than that associated with hepatitis A or B)
      - Acute drug-induced hepatitis
      - Acute circulatory failure (ischaemic liver injury)
      - Exacerbations of chronic hepatitis
    - 2–10 times rise occurs in:
      - Infectious mononucleosis
      - Cytomegalovirus infections
    - Less than five fold rise occurs in:
      - Alcoholic hepatitis (AST:ALT ratio >2)
      - Obstructive jaundice
      - Cirrhosis of liver
      - Non-alcoholic fatty liver
      - Chronic hepatitis
  - Pyridoxal 5′-phosphate is a coenzyme required for synthesis of transaminases especially ALT. This enzyme is deficient in alcoholic patients; hence, AST:ALT ratio is more than 2 in patients with alcoholic liver disease.
- Aspartate aminotransferase (AST).
  - AST exists as two different isoenzymes: mitochondrial and cytoplasmic form.
  - AST is found in highest concentration in heart compared with other tissues of the body such as liver, skeletal muscle and kidney.
  - Elevated mitochondrial AST is seen in extensive tissue necrosis during myocardial infarction and also in acute and chronic liver diseases.
  - About 80% of AST activity of liver is contributed by mitochondrial isoenzyme, whereas most of circulating AST activity in normal people is derived from cytosolic isoenzyme.
  - A ratio of AST/ALT is >5, especially if ALT is normal or slightly elevated, is suggestive of injury to extrahepatic tissues, such as skeletal muscle in the case of rhabdomyolysis or strenuous exercise.
  - ALT is present in highest concentration in periportal hepatocytes and in lowest concentration in hepatocytes surrounding the central vein. AST is present in hepatocytes at more constant levels.
  - Hepatocytes around the central vein have the lowest oxygen concentration and thus are more prone to damage in the setting of acute hepatic ischaemia which results in AST value greater than ALT.
  - After there is no further injury to hepatocytes, rate of decline of AST and ALT depends on their rate of clearance from the circulation. Plasma half-life of ALT is nearly three times that of AST. Hence AST declines more rapidly than ALT, and ALT may be higher than AST in the recovery phase of injury.

(B) Alkaline Phosphatase (ALP)

- Serum contains ALP activity derived from liver, bone, intestines, proximal tubules of kidneys and placenta. Normal serum level is 3–13 KA units (80–240 IU/L).
- In hepatocellular jaundice, only very small amount of ALP is liberated from the cells and the rise in ALP is less than 2½ folds.
- In obstructive jaundice, due to obstruction of biliary tract at any level, new ALP is synthesised that escapes into blood. Hence, ALP levels are markedly raised in obstructive jaundice.

- If the source of ALP is not clear, determine the levels of two enzymes, γ-glutamyl transpeptidase and 5'-nucleotidase. These are more specific for liver. The associated elevation of these two enzymes confirms the source of ALP as liver. Other causes of raised ALP are given in the information box:

• Infiltrative disorders of liver (sarcoidosis, tuberculosis, lymphomas) • Cholestasis • Biliary cirrhosis • Adolescence • Rickets • Sepsis	• Metastatic bone tumours • Paget's disease • Hyperparathyroidism • Pregnancy • Tumours of GI tract • Drugs (antibiotics, antiepileptics and anabolic steroids) • Total parenteral nutrition

- Low levels of ALP can be present in patients with fulminant Wilson disease, hypophosphatasia and haemolytic anaemia.

(C) γ-Glutamyl Transpeptidase (GGT)

- GGT is a microsomal enzyme present in hepatocytes and biliary epithelial cells, renal tubules, pancreas and intestine.
- Raised levels occur in biliary obstruction and parenchymal damage, but not in patients with bone disease.
- But more important is its rise in acute alcoholism. So, it is useful to detect and follow alcohol abuse in patients who deny it. Raised levels suggest prolonged intake of more than 60 g alcohol/day.
- Other causes of elevated GGT include non-alcoholic fatty liver, chronic obstructive lung disease, diabetes mellitus, hyperthyroidism, obesity and renal failure. Also raised in patients taking barbiturates or phenytoin.

Plasma Proteins

- Albumin is synthesised in liver. In chronic liver diseases like cirrhosis and chronic hepatitis, serum albumin is low. Fall indicates severe liver cell damage and bad prognosis. Normal serum albumin level is 4–5.5 g/100 mL.
- Globulins are synthesised by the reticuloendothelial system. Its level rises in chronic liver diseases. Normal serum globulin level is 1.5–3.5 g/100 mL.
  - IgG is mainly raised in chronic hepatitis and cryptogenic cirrhosis.
  - IgA is mainly raised in alcoholic liver disease.
  - IgM is mainly raised in primary biliary cirrhosis.
- Plasma protein electrophoresis shows characteristic changes in cirrhosis with decrease in albumin and increase in γ-globulin.

Coagulation Factors

- Liver synthesises all the coagulation factors except factor VIII. Vitamin K is required to activate some factors. Prothrombin time depends on factors I, II, V, VII and X and it gets prolonged when the plasma concentration of any one of these falls below 30% of normal.
- Among vitamin K-dependent factors, factor VII is the most sensitive marker of liver injury due to shortest half-life time.
- Prothrombin time (normal value 11–12.5 seconds) is prolonged in:
  - Severe liver damage as in acute hepatitis, e.g. viral hepatitis.
  - Prolonged biliary obstruction that reduces vitamin K absorption.
  - Deficiency of vitamin K (including malabsorption, poor intake and antibiotic therapy which produces destruction of vitamin K-producing commensals).
  - Consumption coagulopathy.

Ceruloplasmin

- Synthesised in liver and is an acute phase reactant.
- It binds with copper and serves as a major carrier for copper in the blood.
- Normal plasma level of ceruloplasmin is 20–60 mg/dL.
- Levels are elevated in infections, rheumatoid arthritis, pregnancy, liver diseases and obstructive jaundice.

- In Wilson's disease, ceruloplasmin level is depressed due to decreased rate of synthesis. Low levels may also be seen in neonates, Menke's disease, kwashiorkor, marasmus, protein-losing enteropathy and copper deficiency.

Bromsulphthalein (BSP) Clearance

- BSP clearance is delayed in Dubin–Johnson syndrome. Not done at present.

Liver function tests—summary	
- Bilirubin	Transport
- Aminotransferases	Hepatocellular damage
- Alkaline phosphatase (ALP)	Biliary tract obstruction
- γ-glutamyl transpeptidase (GGT)	Enzyme induction
- Proteins	Synthesis
- Coagulation tests	Synthesis

Q. Write a short note on alpha-foetoprotein.

- α-foetoprotein is mainly synthesised in foetal liver. Its production falls to low levels after birth.
- Re-appearance of substantial concentrations of α-foetoprotein during adult life and increased concentrations in chronic liver disease suggest the development of hepatocellular carcinoma (hepatoma).
- Conditions associated with elevated levels of α-foetoprotein are:
    - Hepatocellular carcinoma
    - Carcinomas of stomach, pancreas, gall bladder, bile ducts and lungs
    - Embryonic carcinomas
    - Viral hepatitis
    - Chronic hepatitis
    - Cirrhosis.

Q. Briefly discuss the indications and significance of liver biopsy.

- In cirrhosis.
    - Clinical suspicion but not LFT proved.
    - Differentiate between various forms of cirrhosis.
    - Diagnosis of fatty liver without fibrosis from cirrhosis.
- Diagnosis of hepatic malignancy like primary (hepatoma) and secondaries.
- In chronic hepatitis (for diagnosis but more often for assessing the severity and stage of liver damage, and response to treatment).
- Diagnosis of granulomatous diseases like tuberculosis, leprosy and sarcoidosis.
- Storage and metabolic disorders like amyloidosis, glycogen storage disorders, haemochromatosis and Wilson's disease.
- Pyrexia of unknown origin (when associated with hepatomegaly).
    - Brucellosis
    - Tuberculosis
    - Cholangitis
    - Lymphoproliferative malignancies.
- Acute jaundice—in cases where even after 3 weeks diagnosis is not obvious on routine biochemical grounds.
- Operative liver biopsy done in staging of lymphoma.
- After liver transplantation a liver biopsy is highly valuable to assess for rejection and the presence and intensity of disease recurrence.

Q. Enumerate the contraindications of liver biopsy.

- Coagulation disorders	- Prolonged prothrombin time
- Severe jaundice	- Haemangioma of liver
- Ascites (gross)	- Hydatid cyst
- Hepatobiliary infections	- Hepatocellular failure

Q. What is hepatic elastography? Explain briefly.

- Conventional liver tests and imaging studies are not sensitive for hepatic fibrosis, which is an early stage of chronic liver disease and cirrhosis.
- Hepatic elastography is a method for measurement of hepatic fibrosis in a non-invasive way.
- Can be accomplished by ultrasound or magnetic resonance.
- Useful to:
  - Estimate existing degree of liver damage.
  - Monitor disease progression or regression via serial measurements.
  - Guide prognosis and further management including treatment.

Ultrasound Elastography

- Uses a mild amplitude, low frequency (50 Hz) vibration transmitted through the liver. It induces an elastic shear wave that is detected by pulse echoultrasonography as the wave propagates through liver. The velocity of wave correlates with tissue stiffness; the wave travels faster through denser, fibrotic tissue.
- Can sample a much larger area than liver biopsy, providing a better understanding of the entire hepatic parenchyma. Moreover, it can be repeated often without risk.
- Less effective in obese patients as adipose tissue attenuates the elastic wave.
- May overestimate degree of fibrosis in:

  - Liver inflammation (e.g. active hepatitis)
  - Cholestasis (e.g. biliary obstruction)
  - Mass lesions within the liver (e.g. tumour)
  - Liver congestion (e.g. heart failure)

Magnetic Resonance Elastography

- Possibly more reliable than ultrasound elastography.

Q. Explain endoscopic retrograde cholangiopancreatography (ERCP).

- The facilities provided by ERCP include the following:
  - Direct visualisation and manipulation of the papilla of Vater.
  - Manipulations within the common bile duct using balloon catheters, wire baskets and stents.
  - Radiological imaging of biliary tree and pancreatic duct.
- Uses:
  - Biopsy of ampullary carcinoma
  - Anatomical study of biliary tree and pancreatic duct in cholestasis of unknown cause
  - Removal of stones from CBD
  - Biliary drainage in malignant strictures.
  - Dilatation of benign strictures.
- Complications:
  - Pancreatitis
  - Cholangitis
  - Bleeding
  - Duodenal perforation.

Q. Give a brief account of uses and complications of percutaneous transhepatic cholangiography (PTC).

- Procedure involves passing a Chiba needle into the liver under screening and injecting contrast material directly into an intrahepatic bile duct. This delineates the entire biliary tract. Not commonly used at present.
- Uses:
  - Documentation and localisation of the site of obstruction of the biliary tract
  - Pre-operative planning of surgery
  - Stent introduction in malignant strictures.

- Complications:
  - Bleeding
  - Infection
  - Biliary peritonitis.

Q. Write briefly on magnetic resonance cholangiopancreatography (MRCP).

- Has largely replaced diagnostic ERCP.
- MR imaging is used to visualise fluid in biliary and pancreatic ducts as high signal intensity on T2-weighted sequences.
- MRCP is comparable to invasive ERCP for diagnosis of extrahepatic bile duct and pancreatic duct abnormalities such as choledocholithiasis, malignant obstruction of bile and pancreatic ducts, congenital anomalies and chronic pancreatitis.
- Other indications for MRCP usually include unsuccessful ERCP or a contraindication to ERCP.
- It is a little inferior to ERCP in diagnosis of sclerosing cholangitis.

Q. Write a short note on endoscopic ultrasound (EUS).

- Gradually replacing ERCP as a diagnostic modality.
  - Useful in imaging pancreatic and biliary diseases such as choledocholithiasis, pancreatic and biliary cancers and cystic lesions of the pancreas.
  - In ampullary carcinoma, local tumour extension and regional lymph node metastasis can be evaluated by EUS and not by ERCP.
- Fine needle aspiration can be performed from suspicious lesions under EUS guidance.
- It is also being increasingly used for interventions.
  - Injection of bupivacaine and alcohol into the coeliac ganglia to reduce pain in patients with unresectable pancreatic carcinoma.
  - Endoscopic management of pancreatic pseudocysts.
  - Biopsy of mediastinal lymph nodes.
- Disadvantages:
  - High cost
  - High degree of training required.
  - Possibility of missing small stones in the common bile duct.
  - Pigment stones may not produce any shadowing and may be missed.
  - Cannot differentiate benign from malignant tumours at the ampulla of Vater.

Q. What are the sources of bilirubin? Discuss the metabolism of bilirubin.

- Bilirubin metabolism can be discussed under the following headings:
  - Normal sources of bilirubin
  - Transport of bilirubin
  - Hepatic metabolism
  - Intestinal phase of bilirubin metabolism
  - Renal excretion of bilirubin.

Normal Sources of Bilirubin

- 80–85% of bilirubin is derived from the catabolism of the haemoglobin of senescent red blood cells.
- 15–20% is derived from bone marrow due to the destruction of maturing cells and from liver due to the turnover of haem and haem containing precursors (cytochromes, myoglobin, etc.).
- Haem liberated from above sources is oxidised to biliverdin by the enzyme haem oxygenase.
- Biliverdin is then reduced to bilirubin by the enzyme biliverdin reductase.

Transport of Bilirubin

- Unconjugated bilirubin is liberated into plasma. This unconjugated bilirubin is tightly bound to albumin in a fully reversible manner. Thus, unconjugated bilirubin is transported in the plasma and bound to albumin. Unbound unconjugated bilirubin can cross blood–brain barrier and cause kernicterus in neonates with hyperbilirubinaemia.
- Conjugated bilirubin is also bound to albumin, but both in reversible and irreversible manner.

Hepatic Metabolism

- It has three distinct phases:
  - Hepatic uptake
  - Conjugation
  - Excretion into bile.

Hepatic Uptake

- Unconjugated bilirubin-albumin complex is subjected to the liver cell, i.e. hepatocyte. Albumin dissociates and the unconjugated bilirubin enters the cell. In the cell, unconjugated bilirubin gets bound to several of the glutathione-S-transferases, formally called ligands. This binding prevents the efflux of unconjugated bilirubin back into plasma.

Conjugation

- In the hepatocyte, the unconjugated bilirubin is conjugated by the enzyme bilirubin UDP-glucuronosyltransferase (UGT1A1). The cosubstrate for bilirubin conjugation is UDP-glucuronic acid, a ubiquitous intracellular substance derived from glucose.
- Conjugation is a two-step reaction resulting first in the formation of bilirubin monoglucuronide and then bilirubin diglucuronide.
- Why conjugate? Unconjugated bilirubin is water-insoluble and so not excreted into bile. So, it must be converted to a water-soluble derivative (i.e. conjugated bilirubin or bilirubin glucuronide) in order to be excreted by the liver cell into bile.

Excretion or Secretion into Bile

- This is the rate limiting step of bilirubin metabolism. This step is the one that is most susceptible to impairment when liver cell is damaged.
- The secretion across the plasma membrane is by an ATP-dependent transport process mediated by a canalicular membrane protein called multidrug resistance-associated protein 2 (MRP2).
- So conjugated bilirubin is secreted into bile. Normal bile contains 90% of bilirubin diglucuronide and 7% of bilirubin mono-glucuronide with remaining 2–3% as unconjugated bilirubin.
- When this step is compromised two consequences occur:
  1. Decreased excretion of bilirubin into bile.
  2. Regurgitation or re-entry of conjugated bilirubin into the blood stream (conjugated hyperbilirubinaemia).

Alb—Albumin
B—Unconjugated bilirubin
BMG—Bilirubin monoglucuronide
BDG—Bilirubin diglucuronide
UGT1A1—UDP-glucuronosyltransferase
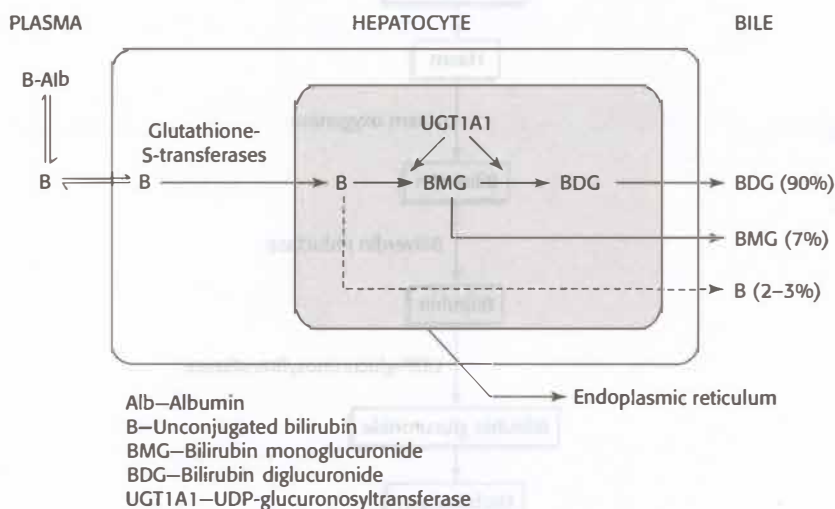
Intestinal Phase of Bilirubin Metabolism

- Conjugated bilirubin (bilirubin diglucuronide and bilirubin monoglucuronide) reaches the intestinal lumen through bile. Conjugated bilirubin as such is not reabsorbed by the intestinal mucosa.

- This conjugated bilirubin has got two fates:
  1. Part of this conjugated bilirubin is excreted in the stool as such, i.e. bilirubin diglucuronide and bilirubin monoglucuronide.
  2. Rest of the conjugated bilirubin is metabolised in the lumen to urobilinogen by the action of intestinal bacteria. This urobilinogen has three fates:
     a. Part of this urobilinogen is reabsorbed from small intestine into the portal circulation, thus reaching liver (enterohepatic circulation). The liver re-excretes this urobilinogen into bile.
     b. Part of the urobilinogen is reabsorbed and excreted in the urine as urobilinogen (up to 4 mg/day).
        - So normal urine contains urobilinogen.
        - In obstructive jaundice urobilinogen is absent in the urine.
        - In hepatocellular disease or haemolytic disease, urinary urobilinogen is increased markedly (more than 4 mg/day).
     c. Part of the urobilinogen in the intestine is excreted in the stool as stercobilinogen. Stercobilinogen gives the stool its normal colour. In obstructive jaundice stercobilinogen is absent in the stool, and hence stools are pale or clay coloured.

Renal Excretion of Bilirubin

- In normal individuals, there is no bilirubin in urine since unconjugated bilirubin is tightly bound to albumin and hence not filtered by glomeruli.
- But with regard to conjugated bilirubin, a small fraction (5%) is less tightly bound to albumin and another small fraction is unbound. This unbound fraction is filtered and appears in the urine as bilirubin (bilirubinuria).
- So in contrast to unconjugated hyperbilirubinaemia, bilirubin appears in the urine in conjugated hyperbilirubinaemia (obstructive jaundice).

Bilirubin Metabolism—Summary
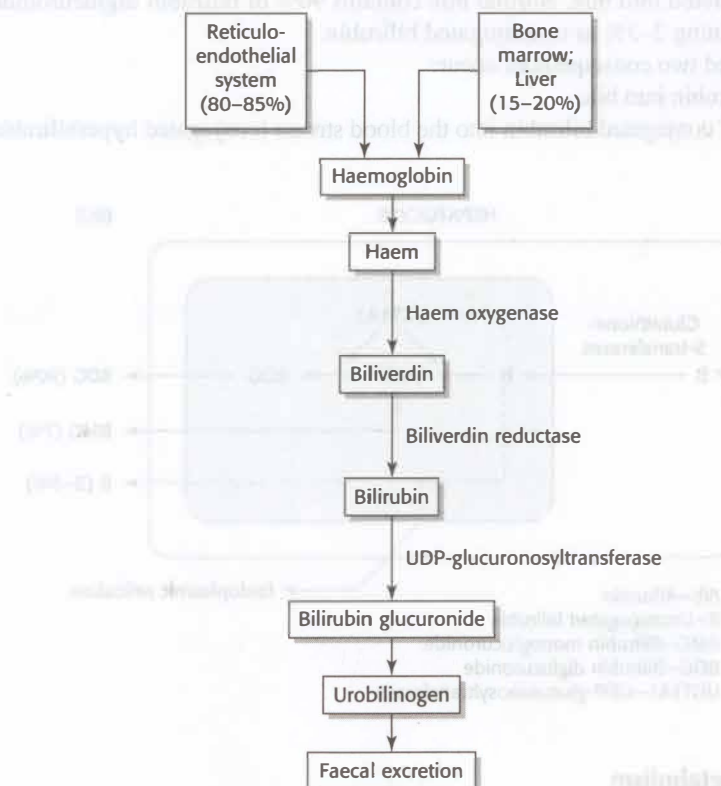
Q. Briefly discuss Van den Bergh reaction.

- It is meant to measure the levels of conjugated and unconjugated bilirubin in the blood.
- Unconjugated bilirubin requires the presence of alcohol for the reaction while conjugated bilirubin reacts directly without alcohol. Hence conjugated bilirubin is also referred to as direct bilirubin and unconjugated bilirubin as indirect bilirubin.
- Three steps involved are:
  a. Measure total serum bilirubin (unconjugated plus conjugated) by carrying out the reaction in alcohol.
  b. Measure direct reacting bilirubin (conjugated) by carrying out the test without alcohol.
  c. Calculate indirect reacting bilirubin (unconjugated bilirubin) by finding the difference between total and conjugated bilirubin.
- Based on the van den Bergh reaction, the hyperbilirubinaemias can be classified into two types:
  a. Predominantly unconjugated hyperbilirubinaemia—where 80–85% of total serum bilirubin is measured as indirect reacting (unconjugated).
  b. Predominantly conjugated hyperbilirubinaemia—where more than 50% of total serum bilirubin is of direct reacting type (conjugated).

Q. Enumerate the causes of jaundice. How will you arrive at the aetiology of jaundice? Give the points of differentiation in clinical features and investigations.

Definition

- Jaundice is defined as yellowish pigmentation of skin, mucous membrane and sclera by bilirubin, resulting from elevated levels of bilirubin in the blood. Scleral pigmentation is due to the richness of this tissue in elastin that has a special affinity for bilirubin.
- Carotenaemia is characterised by yellowish pigmentation of skin by carotene but not of sclera.
- Clinical jaundice occurs when serum bilirubin is more than 2.5 mg/dL (normal is 0.3–1.0 mg/dL).
- Unilateral jaundice (in the limbs) is seen in hemiplegia and unilateral oedema. The hemiplegic and oedematous limbs may remain uncoloured.

Classification

- Jaundice can be classified in two ways:
  1. Based upon the underlying derangement of bilirubin metabolism.
  2. Based upon the pathological mechanism giving rise to jaundice.

Classification Based upon the Underlying Derangement of Bilirubin Metabolism

- Predominantly unconjugated hyperbilirubinaemia
- Predominantly conjugated hyperbilirubinaemia

Predominantly unconjugated	
• Overproduction	Haemolysis, ineffective erythropoiesis, reabsorption of large haematoma
• Decreased hepatic uptake	Drugs (e.g. flavaspidic acid), sepsis
• Decreased conjugation	Gilbert's syndrome, Crigler–Najjar syndrome, neonatal jaundice, acquired transferase deficiency (e.g. cirrhosis, hepatitis)
Predominantly conjugated	
• Intrahepatic causes	
• Familial and hereditary	Dubin–Johnson syndrome, Rotor syndrome, recurrent benign intrahepatic cholestasis, cholestatic jaundice of pregnancy
• Acquired disorders	Hepatocellular diseases, drug-induced cholestasis
• Extrahepatic causes	Stone in common bile duct, tumours and strictures of bile duct, periampullary carcinoma, carcinoma head of pancreas

Note:

In hepatocellular disease (cirrhosis and hepatitis) there is usually interference in all three major steps of bilirubin metabolism—uptake, conjugation and excretion. However, excretion is the rate-limiting step, and is usually impaired to the greatest extent. As a result conjugated hyperbilirubinaemia predominates.

Classification of Jaundice Based on the Pathological Mechanism Giving Rise to Jaundice

- Haemolytic jaundice
- Hepatocellular jaundice
- Cholestatic jaundice

Haemolytic Jaundice

- Results from increased destruction of red blood cells or their precursors, resulting in increased bilirubin production.
- Unconjugated bilirubin accumulates in the plasma.

Causes of Haemolysis

- Intraerythrocytic defects	
- Hereditary	Spherocytosis, sickle cell disease, thalassaemia, G6PD deficiency
- Acquired	B_{12} and folate deficiency
- Extraerythrocytic defects	Antibodies (autoimmune and isoimmune haemolytic anaemias), malaria, prosthetic heart valves, drugs like sulphasalazine and dapsone, paroxysmal nocturnal haemoglobinuria

Clinical Features

- Pallor due to anaemia.
- Jaundice is mild; no other signs of liver disease.
- Hepatosplenomegaly due to increased reticuloendothelial activity.
- Dark stools due to increased stercobilinogen.
- Urine turns dark yellow on standing due to increased urobilinogen in the urine getting converted to urobilin.

Investigations

- No bilirubin in urine.
- Urinary urobilinogen is increased (more than 4 mg/24 hours).
- Serum bilirubin is raised (less than 6 mg/dL).
- Predominantly unconjugated hyperbilirubinaemia.
- Other liver function tests are normal.
- Evidence of haemolytic anaemia.

Hepatocellular Jaundice

- Bilirubin transport across the hepatocyte may be impaired at any point between the uptake of unconjugated bilirubin into the cell and transport of conjugated bilirubin into biliary canaliculi.
- In addition, swelling of cells and oedema due to inflammation cause mechanical obstruction of intrahepatic biliary tree.
- Hence in hepatocellular jaundice, concentration of both unconjugated and conjugated bilirubin rises in the blood.

Causes

- Viral hepatitis	- Drug-induced hepatitis
- Alcoholic hepatitis	- Chlorpromazine, imipramine
- Chronic hepatitis	- INH, rifampicin, erythromycin
- Cirrhosis	- Amitriptyline, halothane, methyldopa

Cholestatic Jaundice

- Cholestasis means failure of bile flow, and its cause may lie anywhere between hepatocyte and duodenum.
- Cholestatic jaundice is usually a "surgical jaundice".
- Cholestasis can be due to small duct obstruction (intrahepatic cholestasis) or large duct obstruction (extrahepatic cholestasis).

- The consequences are retention of bile acids and bilirubin in the liver and blood, and a deficiency of bile acids in the intestine.

Causes

Small duct obstruction (intrahepatic cholestasis)	Large duct obstruction (extrahepatic cholestasis)
• Drugs, alcohol	• Gall stones in the CBD
• Viral hepatitis, cirrhosis	• Carcinoma head of pancreas
• Chronic hepatitis	• Carcinoma ampulla of Vater
• Primary biliary cirrhosis	• Stricture of bile ducts
• Severe bacterial infections	• Sclerosing cholangitis
• Hodgkin's disease	• Helminths in the CBD
• Granulomas (tuberculosis, sarcoidosis)	• Carcinoma of bile ducts
• Widespread secondaries in liver	**Inborn errors of bile secretion**
• Ulcerative colitis	• Progressive familial intrahepatic cholestasis
• Hypotension	• Benign recurrent intrahepatic cholestasis
• Total parenteral nutrition	
• Pregnancy	

Clinical Features
- Symptoms:
  - Jaundice (gradually progressive or fluctuating)
  - Pruritus
  - Pale or clay-coloured stools
  - Dark urine (increased conjugated bilirubin)
  - Fever with chills and rigors (cholangitis)
  - Weight loss (malabsorption)
  - Haemorrhagic tendency (vitamin K deficiency)
  - Bone pains (calcium and vitamin D deficiency)
  - Abdominal pain.
- Signs:
  - Deep jaundice with a greenish hue
  - Scratch marks
  - Xanthelasmas on eyelids (lipid deposit)
  - Xanthomas over tendons (lipid deposit)
  - Palpable gall bladder (in carcinoma head of pancreas)
  - Large hard irregular liver (neoplasm)
  - Secondary biliary cirrhosis (late)
  - Signs of liver cell failure (late).

Investigations
- Bilirubin present in urine.
- Urobilinogen absent in urine.
- Serum bilirubin markedly raised.
- Predominantly conjugated hyperbilirubinaemia.
- Serum ALP markedly raised (>3–4 times that of normal).
- Minimal biochemical changes of parenchymal damage.
- Ultrasonography (for underlying cause).
- Antimitochondrial antibody (primary biliary cirrhosis).
- ERCP or MRCP.
- Percutaneous transhepatic cholangiography (PTC).
- Liver biopsy (only if there is evidence of liver cell disease).

Q. How do you clinically differentiate haemolytic jaundice, hepatocellular jaundice and obstructive (cholestatic) jaundice?

Clinical Features of Jaundice—Summary

Clinical feature	Haemolytic	Hepatocellular	Obstructive
• Colour of jaundice	Lemon yellow	Orange yellow	Greenish yellow
• Depth of jaundice	Mild	Variable	Deep
• Pruritus	Absent	Variable	Present
• Bleeding tendency	Absent	Present	Present (late)
• Bradycardia	Absent	Absent	Present
• Anaemia	Present	Absent	Absent
• Splenomegaly	Present	Variable	Absent (late; after cirrhosis)
• Palpable gall bladder	Absent	Absent	May be present
• Features of hepatocellular failure	Absent	Present (early)	Present (late)

Q. Discuss briefly the congenital non-haemolytic hyperbilirubinaemias.

Congenital Non-Haemolytic Hyperbilirubinaemias

- Gilbert's syndrome
- Crigler–Najjar syndrome type I
- Crigler–Najjar syndrome type II
- Dubin–Johnson syndrome
- Rotor syndrome

Gilbert's Syndrome

- Aetiology:
  - Mild deficiency of UGT1A1 (reduced to 10–35% of normal) enzyme resulting in unconjugated hyperbilirubinaemia.
  - Autosomal dominant inheritance.
- Clinical features:
  - More common in males; occurs in 5% of general population.
  - Usually asymptomatic and jaundice detected incidentally.
  - Rarely symptoms like anorexia, malaise and upper abdominal pain occur.
  - Depth of jaundice increases with infections, fatigue, exertion and fasting. During fasting, glucose is depleted that results in lower availability of UDP–glucuronic acid required for conjugation.
  - Physical examination is normal, except for mild jaundice.
- Investigations:
  - Unconjugated hyperbilirubinaemia (less than 6 mg/dL). Elevation of bilirubin levels during fasting is used as the most common diagnostic tool. Following reduced calorie intake of 400 kcal/day for 24–48 hours a significant increase in bilirubin blood levels is usually observed.
  - Urobilinogen in the urine is increased.
  - No bilirubinuria.
  - Normal peripheral smear, reticulocyte count and serum haptoglobin.
- Treatment:
  - Usually no treatment is necessary.
  - Glucuronosyl-transferase activity may be increased by phenobarbital 60 mg BD.

Crigler–Najjar Syndrome Type I

- Autosomal recessive inheritance.
- Complete absence of bilirubin-uridine diphosphate-glucuronosyl-transferase, and therefore bile is colourless.
- Severe unconjugated hyperbilirubinaemia and kernicterus lead to death.
- Treatment includes daily phototherapy and liver transplantation. Phenobarbitone has no effect.

Crigler–Najjar Syndrome Type II

- Autosomal recessive inheritance in most cases.
- Partial deficiency of UGT1A1 (<10% of normal).
- Jaundice is milder than type I (bilirubin 6–25 mg/dL), no kernicterus.
- Treatment includes ultraviolet light therapy, phenobarbitone and in some cases, liver transplantation.

Dubin–Johnson Syndrome

- Autosomal recessive inheritance.
- Reduced ability to transport bilirubin diglucuronide into biliary canaliculi.
- The syndrome is due to defective MRP2, which is required for secretion of conjugated bilirubin from the hepatocytes into canaliculi.
- Clinically presents with jaundice, generally after puberty.
- Conjugated hyperbilirubinaemia (usually 2–5 mg/dL) and bilirubinuria.
- The degree of hyperbilirubinaemia may be increased by intercurrent illness, oral contraceptives and pregnancy.
- Life expectancy is generally normal.
- Gall bladder is usually not visualised on oral cholecystography.
- BSP (bromosulphthalein) retention test shows impaired clearance with reflux into blood at 90 minutes.
- Liver biopsy shows dark pigment in centrilobular hepatocytes.
- No treatment is required in most cases.

Rotor Syndrome

- Autosomal recessive inheritance.
- Due to poor uptake and storage of bilirubin by liver cells.
- Clinical presentation is with mild jaundice.
- Conjugated hyperbilirubinaemia and bilirubinuria.
- BSP retention test shows impaired clearance but there is no reflux back into blood.
- Gall bladder is visualised on oral cholecystography.
- Liver biopsy is normal and does not show dark pigment.

Q. Explain briefly about Charcot's triad.

- The presence of following triad in the presence of stones in bile ducts: 1. Pain in the right hypochondrium. 2. Intermittent or persistent jaundice. 3. Fever with chills and rigors due to acute cholangitis.

Q. Describe Courvoisier's law.

- In common bile duct obstruction with stone, the gall bladder as a rule is impalpable. Most patients with jaundice due to stones have a shrivelled, fibrotic, non-distensible gall bladder, and hence gall bladder will not be palpable.
- A jaundiced patient with malignant obstruction (e.g. carcinoma head of pancreas) will have distensible gall bladder, and hence gall bladder may be palpable.

Q. Write a short note on drug- and toxin-induced liver injury.

- Two major types of chemical hepatotoxicity have been recognised: 1. Direct toxic type. 2. Idiosyncratic type.
- Direct toxic hepatitis is characterised by a predictable and dose-related toxicity, short latent period and absence of extra-hepatic manifestations.
- Idiosyncratic drug reactions are characterised by unpredictable, most often dose-independent toxicity with variable latent period and presence of extrahepatic manifestations like fever, rashes, arthralgia and eosinophilia. However, for many drugs, idiosyncratic hepatotoxicity can be dose dependent. Drugs causing this type of reaction include halothane, isoniazid and chlorpromazine.
- Severity may range from asymptomatic elevations of hepatic enzymes to chronic liver disease to fulminant hepatic failure.
- Treatment:
  - Withdrawal of the suspected agent.
  - Mainly supportive therapy as in viral hepatitis.

Common Hepatotoxic Drugs and Toxins with Morphologic Changes

Cholestasis
- Methyltestosterone
- Methimazole
- Erythromycin estolate

- Chlorpropamide
- Chlorpromazine
- Anabolic steroids
- Cyclosporin INimesulide
- Amoxicillin/clavulanate

Fatty liver
- Zidovudine
- Amiodarone
- Indinavir
- Ritonavir
- Methotrexate
- Tetracyclines
- Valproic acid

Toxic (necrosis)
- Paracetamol
- Carbon tetrachloride
- Yellow phosphorus
- Mushroom (*Amanita phalloides*)

Hepatitis
- Halothane
- Phenytoin
- Methyldopa

- Isoniazid
- Rifampicin
- Ibuprofen
- Ketoconazole
- Fluconazole
- Zidovudine
- Chlorothiazide
- Oxyphenisatin

Granulomas
- Phenylbutazone
- Sulphonamides
- Allopurinol
- Carbamazepine
- Quinidine

Hepatic fibrosis
- Methotrexate

Chronic hepatitis
- Phenytoin
- Isoniazid

Q. Describe the aetiology, epidemiology, pathogenesis, clinical features and treatment of viral hepatitis. Add a note on the diagnosis and prevention.

Q. Give a brief account of aetiology and epidemiology of delta hepatitis.

Q. Briefly describe anicteric hepatitis.

Types of Viral Hepatitis

Hepatitis caused by common viruses	Hepatitis caused by other viruses
• Hepatitis A, caused by hepatitis A virus (HAV)	• Cytomegalovirus
• Hepatitis B, caused by hepatitis B virus (HBV)	• Epstein–Barr virus
• Delta hepatitis, caused by hepatitis D virus (HDV)	• Herpes simplex virus
• Hepatitis C, caused by hepatitis C virus (HCV)	• Yellow fever virus
• Hepatitis E, caused by hepatitis E virus (HEV)	• Hepatitis G virus

Hepatitis A

Aetiology
- Caused by hepatitis A virus (HAV), a RNA virus belonging to the picornavirus group.
- HAV survives on human hands and fomites, and requires temperatures higher than 185°F (85°C) for inactivation. It is resistant to freezing, detergents and acids, but it is inactivated by formalin and chlorine.

Epidemiology
- Incubation period is 30 days (15–45 days).
- Source of the infection is persons incubating or suffering from the disease.
- HAV is transmitted almost exclusively by the faecal-oral route. Infected persons excrete the viruses in their faeces for 2 weeks before the onset and 5–7 days after the onset of the illness.

- Can rarely be spread by blood transfusions and homosexual activity.
- Children are most commonly affected. Overcrowding and poor sanitation facilitate the spread.
- In outbreaks, water, milk and shell fish are all implicated.
- No carrier state has been identified.
- The single most important predictor of the clinical course of an acute hepatitis A infection is the age. Symptomatic infections are uncommon in young children. In adults 75–90% of the infections are symptomatic, with jaundice in majority of cases.

Prevention

- At community level prevention is attempted by improving social conditions, especially overcrowding and unhygienic situations.
- Immune serum globulin (0.02 mL/kg) can protect from infection for 3 months. It is used in those at particular risk, e.g. close contacts, those with other major diseases, pregnant females and in outbreaks, for example, in a school or nursery. The course of HAV infection may be modified through the appropriate use of human immunoglobulin. In household contacts passive prophylaxis with immunoglobulin within 2 weeks of exposure reduces icteric disease by more than 80%, although the infection is not necessarily prevented. However, at present, active immunisation rather than passive immunisation is recommended to reduce chances of transmission.
- A vaccine is available for active immunisation. It is approved for use in persons above the age of 2 years. Two doses at 6 month interval are recommended. It seems to provide lifelong immunity. The exact role of this vaccine in Indian setup is not clear as most persons get infection with hepatitis A in early childhood when the disease has a mild course. It may be administered in high-risk groups (military personnel, food handlers). Patients with chronic hepatitis C or other chronic liver diseases may be at an increased risk of fulminant hepatitis or death with HAV superinfection. These patients may be administered HAV vaccine.

Hepatitis B

Aetiology

- Caused by hepatitis B virus (HBV), belonging to the group of hepadna viruses.
- HBV comprises a surface envelope [antigen expressed on it is called hepatitis B surface antigen (HBsAg)] and a nucleocapsid core containing DNA [antigen expressed on its surface is called hepatitis B core antigen (HBcAg), while another soluble antigen in the nucleocapsid is called hepatitis Be antigen (HBeAg)]. Nucleocapsid core also has DNA polymerase enzyme.
- The corresponding antibodies are:
  - Anti-HBs
  - Anti-HBc
  - Anti-HBe.
- HBsAg-positive serum containing HBeAg is more likely to be highly infectious than HBeAg-negative or anti-HBe-positive serum.

Epidemiology

- Incubation period is about 90 days (50–150 days).
- Humans are the only source of infection, being individuals incubating or suffering from acute hepatitis, asymptomatic carriers or persons with chronic liver disease.
- Major route of transmission is parenteral but occasionally non-parenteral.
- Commonly follows transfusion of infected blood or blood products, injections with contaminated needles, intravenous drug use with needle sharing, tattooing and acupuncture. Albumin solutions and gammaglobulins are free of risk. At present, HBV accounts for only less than 10% cases of post-transfusion hepatitis.
- Non-parenteral means of transmission include spread through body fluids like saliva, urine, semen and vaginal secretions. However, this requires close personal contact, sexual intercourse and male homosexuality.
- Mother-to-child spread (perinatal transmission) is also common. It could be either transplacental transmission or transmission at or soon after birth.
- The groups with high-risk rates of HBV infection include spouses of acutely infected persons, sexually promiscuous males (homosexuals), health-care workers exposed to blood, dentists, haemophiliacs and prisoners.
- Risk of transmission of hepatitis B through needle-stick injury from an HBsAg positive person is about 30%.
- A chronic carrier state is described for HBV infection (1–20%).
- Serum HBsAg is positive in 30% cases of Down's syndrome, lepromatous leprosy, leukaemia, Hodgkin's disease, polyarteritis nodosa, patients on chronic haemodialysis and needle using drug addicts.

- The age at which a person is infected with the virus determines the disease outcome; 90% of those who acquire HBV perinatally or in early childhood will develop chronic hepatitis as their immune system cannot destroy and clear infected hepatocytes. In adults, 90% of infections are acute and only 5–10% develop into chronic hepatitis.

Prevention

- For active immunisation recombinant vaccines (containing HBsAg) are available which provide 95% efficacy against HBV infection. Since non-percutaneous routes of transmission are quite prevalent in India, this vaccine is recommended in all children. It is also recommended in high-risk groups (health workers, haemodialysis patients, injection drug users, haemophiliacs and sexual contacts of HBsAg carriers). Injections are given at 0, 1 and 6 months for full immunity. Dose is 10 μg for children under 10 years and 20 μg in children above 10 years. The duration of immunity provided is not known but protective levels of anti-HBs have been found for 5–10 years. Boosters are not recommended at present except in immunosuppressed. The vaccine is not effective in HBsAg carriers.
- Hyperimmune B immunoglobulin (HBIG) is prepared from blood containing anti-HBs. This can prevent or minimise hepatitis B. This should preferably be given within 24 hours or at most a week of exposure. Dose is 0.06 mL/kg. Indications are accidental needle puncture, gross personal contamination with infected blood, oral ingestion or contamination of mucous membranes, and exposure to infected blood in the presence of cuts and grazes.
- Active-passive immunisation is vaccine being given together with hyperimmune globulin, and is recommended for post-exposure prophylaxis in unvaccinated persons. For perinatal exposure of infants born to HBsAg-positive mothers a single dose of 0.5 mL of HBIG in the thigh of newborn immediately after birth is followed by three doses of vaccine starting within 12 hours of birth.

Delta Hepatitis

Aetiology

- Caused by hepatitis D virus (HDV), which is a defective RNA virus. The RNA genome is covered by an outer coat of HBsAg.
- It has no independent existence. It requires HBV for replication and expression.
- HDV can infect a person simultaneously with HBV (coinfection). HDV can superinfect a person who is already a chronic carrier of HBV (superinfection).

Epidemiology

- Two epidemiologic patterns exist: (i) Delta infection being endemic among those with hepatitis B, predominantly transmitted by non-parenteral route, especially close personal contact. (ii) In non-endemic areas, delta infection is confined to persons exposed frequently to blood and blood products, mainly intravenous drug addicts and haemophiliacs. Here, predominant transmission is by parenteral route.
- Coinfection gives rise to severe acute hepatitis that is limited by recovery from HBV infection.
- Superinfection causes rapidly progressive chronic hepatitis, with episodes of acute hepatitis.
- It can cause fulminant liver failure and rapid progression to cirrhosis as well as an increased risk of liver cancer.

Hepatitis C

Aetiology

- Previously called blood-borne non-A, non-B hepatitis.
- It is a single-stranded RNA virus belonging to the family *Flaviviridae*.
- HCV has six genotypes. Chronic HCV 1 infection has poor response to therapy. In India, HCV 3 is most prevalent.
- HCV-RNA can be detected within a few days of infection, well before the appearance of antibodies to HCV (anti-HCV).

Epidemiology

- Incubation period is 50 days (15–160 days).
- Major route of transmission is parenteral.
- More than 90% of cases of post-transfusion hepatitis are caused by HCV. Also common in drug addicts.
- Common sources of infection are blood and blood products capable of transmitting hepatitis B, particularly coagulation factor concentrates. Other modes include perinatal and sexual transmission.
- Transmission of hepatitis C through needle-stick injury is 1–3%.

- HCV is not transmitted by breastfeeding.
- Nearly 80% develop chronic hepatitis (see chronic hepatitis).
- Prevention by vaccine or immunoglobulin not possible.

Hepatitis E

Aetiology

- Previously called epidemic or enterically transmitted non-A, non-B hepatitis.
- It is a single-stranded RNA virus.

Epidemiology

- Incubation period is 40 days (15–60 days).
- Primarily enteric mode of transmission.
- Accounts for epidemic, water-borne hepatitis; common in India.
- Commonly occurs after contamination of water supplies as after monsoon flooding.

Prevention

- Similar to hepatitis A (no vaccine available).

Clinical Features of Viral Hepatitis

- Prodromal symptoms usually last for a few days to 2 weeks before the onset of jaundice, characterised by fever, chills, headache, malaise and prominent gastrointestinal symptoms like anorexia and distaste for cigarettes. Nausea, vomiting and diarrhoea follow. Patients with HBV infection have polyarthralgia and occasionally a "serum sickness syndrome" with skin rashes and polyarthritis.
- Steady upper abdominal pain, sometimes severe (due to stretching of liver capsule).
- Urine is dark with yellowish discolouration of sclera.
- With onset of clinical jaundice constitutional symptoms diminish.
- Liver becomes palpable and tender.
- Enlarged cervical lymph nodes and splenomegaly.
- As obstruction to biliary canaliculi increases (cholestatic phase), jaundice deepens, stools become paler, urine becomes darker and liver becomes more palpable.
- Recovery phase—gradually appetite improves and gastrointestinal symptoms subside; jaundice decreases, stools and urine become normal, and liver size decreases. Over a period of 3–6 weeks, majority recover.
- Recovery phase is more prolonged in acute hepatitis B and hepatitis C.
- Complete clinical and biochemical recovery occurs in 1–2 months from the onset in cases of hepatitis A and E, and in 3–4 months from the onset in hepatitis B and C.
- Delta coinfection is indistinguishable from acute hepatitis B. But delta superinfection appears as a clinical exacerbation resembling acute viral hepatitis in a person chronically infected with HBV. Chronic HDV superinfection is associated with a severe course of hepatitis that frequently leads to rapid fibrosis progression, hepatic decompensation and development of hepatocellular carcinoma.
- In hepatitis A infection, the likelihood of clinically apparent disease increases with age. In children ≤6 years of age most infections (70%) are asymptomatic, and if illness does occur, it is usually anicteric. Among older children and adults infection is usually symptomatic, with jaundice occurring in 70% of patients. In some cases, HAV can cause a second bout of jaundice (relapsing hepatitis) 6–12 weeks after primary infection. There is no evidence of chronic liver disease or persistent infection following HAV infection. However, 15–20% of the patients may have prolonged or relapsing disease lasting up to 6 months. Other atypical features include prolonged cholestasis and acute kidney injury.
- HCV infection is infrequently diagnosed during the acute phase of infection. Most patients (60–75%) are asymptomatic or have mild symptoms.
- In hepatitis B, D and E, fulminant hepatic failure can develop. It is uncommon with hepatitis C and rare in hepatitis A. With hepatitis E, fulminant hepatitis occurs in 1–2% of cases but it occurs in nearly 20% cases in pregnant females.
- Anicteric hepatitis is a mild illness with an anicteric course (no clinical jaundice). Diagnosis is based on the history of contact with a definite case, vague gastrointestinal symptoms, malaise, bilirubinuria and aminotransferase elevation. Diagnosis of anicteric hepatitis needs a high index of suspicion.

Comparison of Hepatitis A, Hepatitis B, Hepatitis C and Hepatitis E

Features	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis E
• Incubation period	30 days (15–45)	90 days (50–150)	50 days (15–150)	40 days (15–60)
• Onset	Acute	Insidious	Insidious	Acute
• Age	Children, young	Any age	Adult, but of any age	Young adults
• Route of transmission				
• Faecal-oral	+++	−	Unknown	+++
• Other non-parenteral	+/−	++	++	+/−
• Parenteral	+	+++	+++	−
• Severity	Mild	Severe	Mild	Mild
• Prognosis	Good	Worse	Moderate	Good
• Chronicity	None	5–10%	50–70%	None
• Prophylaxis	Immune serum globulin	Hyperimmune serum globulin and hepatitis B vaccine	None	None
• Carrier state	None	1–30%	1%	None

Investigations

- Urine shows bilirubinuria (in early stages), slight microscopic haematuria and mild proteinuria.
- Total count is low, with neutropenia, relative lymphocytosis and atypical lymphocytes.
- Aminotransferases (AST, ALT) are raised. Maximum levels are seen in the prodromal phase, varying from 400 to 4000 IU/L. They decline progressively during icteric and recovery phase.
- Bilirubin levels are variably raised. Both conjugated and unconjugated bilirubins are equally raised.
- ALP level may be raised but is usually less than two times the normal.
- Serum protein levels are normal.
- Prothrombin time—marked prolongation signifies extensive hepatocellular damage. This is one of the best indices of prognosis.
- Blood glucose level may be low.
- Antismooth muscle antibody, rheumatoid factor, antinuclear antibody and heterophil antibody may be present in low titres during prodromal phase.

Immunological Tests for Viral Hepatitis

Hepatitis A
- Anti-HAV of the IgM type early in the course (diagnostic of recent infection)
- Anti-HAV of the IgG type later in the course that persists for years conferring immunity

Hepatitis B
- HBsAg—a reliable marker of infection and appears first before the appearance of symptoms. Disappears over 3–6 months
- Anti-HBs—appears after disappearance of HBsAg and persists lifelong. Confers protection against subsequent infection*

- HBcAg—not found in the blood
- Anti-HBc—usually the first antibody to appear and persists lifelong. Initially it is of IgM type and later IgG type
- HBeAg—detected transiently, early in the course. Its persistence is correlated with continued viral replication, infectivity and progression to chronicity
- Anti-HBe—detected later during the course
- HBV-DNA—a marker of active viral replication and appears along with HBsAg

Delta hepatitis
- Delta antigen—occasionally detectable
- Anti-delta—initially of IgM type and later IgG type
- HDV-RNA—most reliable test

Hepatitis C

- Anti-HCV—appears after infection; disappears after recovery; persists in chronic hepatitis C
- HCV-RNA—after exposure, HCV-RNA becomes detectable in serum after 7–14 days, followed by amino-transferase elevation and later (after 4–10 weeks) by presence of antibodies. Remains detectable in most, continuously or intermittently

Hepatitis E

- Anti-HEV—both IgM and IgG are present at onset

*Occasionally, appearance of anti-HBs may trail disappearance of HBsAg by several weeks to months. During this window period both HBsAg and anti-HBs are negative; the sole markers of recent HBV infection during this time are antibodies against the HBV core antigen (IgM and IgG anti-HBc)
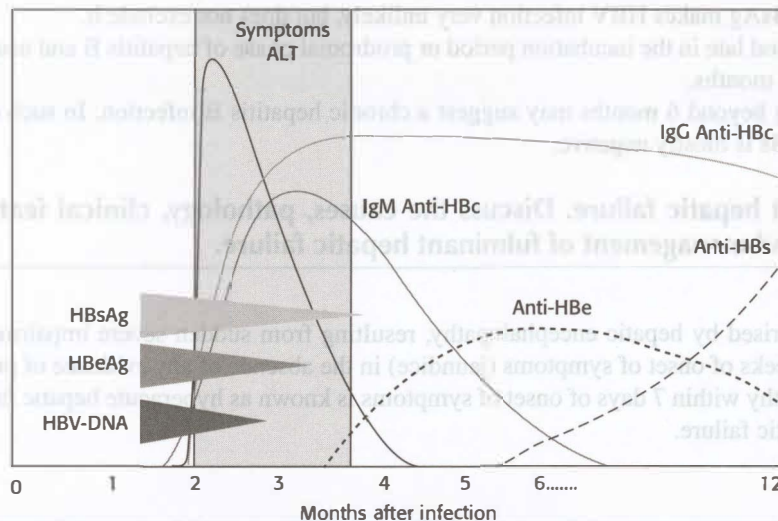
Natural course of hepatitis B infection

Complications of Acute Viral Hepatitis

• Fulminant hepatic failure	• Renal failure
• Relapsing hepatitis	• Henoch–Schonlein purpura
• Cholestatic hepatitis	• Chronic hepatitis
• Post-hepatitis syndrome	• Cirrhosis
• Aplastic anaemia	• Hepatocellular carcinoma
• Polyarteritis nodosa	• Myocarditis
• Transverse myelitis	• Peripheral neuropathy

Poor Prognostic Features

• Marked increase in AST and ALT	• Recurring attacks of hypoglycaemia
• Bilirubin >20 mg/dL	• Renal failure
• Liver not enlarged	• Associated conditions
• Prolongation of prothrombin time by 5 seconds	• HBV, HCV or HDV infection

Treatment

- Rest
  - During the acute symptomatic period, complete rest and thereafter gradual ambulation.
  - In high-risk patients (patients more than 50 years, pregnant and those with other major diseases) rest is continued till symptoms and signs have disappeared, and liver function tests have returned to near normal.
- Diet
  - Nutritious general diet of 2000–3000 kcal/day. In the initial stage, when good diet is not tolerated, give a light diet, fruit drinks and glucose. There is no need to avoid fatty diets, but most patients cannot tolerate these diets.

- Encourage good protein intake.
- If vomiting is severe, intravenous fluids are given.
- Drugs
  - Drugs should be avoided if possible (especially sedatives and hypnotics).
  - Alcohol to be avoided for next 6 months.
  - Oral contraceptives can be resumed after clinical and biochemical recovery.
- Antiviral drugs
  - Some evidence suggests efficacy of interferon-α in patients with acute hepatitis C infection in reducing the rate of chronicity.

Q. Write briefly on Australia antigen, HBsAg or hepatitis B surface antigen.

- HBsAg is located in the capsular material of the virus.
- Identified by haemagglutination and radioimmunoassay methods.
- A negative test for HBsAg makes HBV infection very unlikely, but does not exclude it.
- HBsAg appears in blood late in the incubation period or prodromal phase of hepatitis B and usually lasts for 3–4 weeks or may persist up to 3 months.
- Persistence of HBsAg beyond 6 months may suggest a chronic hepatitis B infection. In such cases anti-HBc remains positive while anti-HBs is mostly negative.

Q. Define fulminant hepatic failure. Discuss the causes, pathology, clinical features, investigations, complications and management of fulminant hepatic failure.

Definition

- A syndrome characterised by hepatic encephalopathy, resulting from sudden severe impairment of hepatic function, occurring within 4 weeks of onset of symptoms (jaundice) in the absence of any evidence of pre-existing liver disease.
- Onset of encephalopathy within 7 days of onset of symptoms is known as hyperacute hepatic failure. It has better prognosis than acute hepatic failure.

Aetiology

- Acute viral hepatitis (B and E)*	- Wilson's disease
- Drugs (refer hepatotoxic drugs)	- Shock
- Pregnancy (acute fatty liver; HELLP**; eclampsia)	- Poisoning, e.g. *Amanita phalloides*, paracetamol
- Autoimmune hepatitis	- Indeterminate (15–20%)

* Fulminant hepatitis is a rare complication of hepatitis A, the risk being <0.5%.
**Co-existence of haemolysis, elevated liver enzymes and low platelets.

Pathology

- Extensive parenchymal necrosis.
- Less than 30% of the liver cells appear viable histologically.
- Severe fatty degeneration in tetracycline toxicity and pregnancy.

Pathogenesis

- Elevated ammonia in the blood apparently plays a role in the pathogenesis of hepatic encephalopathy.
- Other factors implicated include elevated levels of aromatic amino acids, reduced levels of branched-chain amino acids, short-chain fatty acids, mercaptans and false neurotransmitters (octopamine).

Clinical Features

- General features:
  - Weakness, nausea, vomiting
  - Right hypochondrial pain and jaundice
  - Liver may be enlarged initially, but later shrinks and becomes impalpable
  - Liver dullness absent on percussion
  - Ascites and oedema (later).

- Features of hepatic encephalopathy:
  - Reduced alertness, poor concentration, restlessness, manic episodes, drowsiness and coma
  - Confusion, disorientation, inversion of sleep rhythm, yawning, slurred speech and convulsions
  - Foetor hepaticus and flapping tremor (asterixis).
- Features of cerebral oedema:
  - Bradycardia, hypertension and irregular respiration (Cushing's triad)
  - Unequal or abnormally reacting pupils
  - Fixed pupils with spontaneous respiration
  - Hyperventilation and profuse sweating
  - Hyperreflexia and extensor plantars
  - Myoclonus, focal fits and decerebration
  - Papilloedema (late).

Grading of hepatic encephalopathy

•	Grade 1	Trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired addition or subtraction; incoordination, mild asterixis
•	Grade 2	Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behaviour, asterixis
•	Grade 3	Somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation
•	Grade 4	Coma (unresponsive to verbal or noxious stimuli); decerebration

- Other features:
  - Coagulopathy resulting in bleeding from various sites including intracranial bleed.

Investigations

- Urine contains protein, bilirubin and urobilinogen.
- Leucocytosis, thrombocytopenia.
- Serum bilirubin is raised.
- Serum aminotransferase activity is initially raised but falls later.
- Hypoalbuminaemia.
- Prothrombin time is prolonged.
- Blood ammonia levels are elevated.
- Plasma and urine amino acids are increased.
- EEG—characteristic of hepatic encephalopathy.
- Ultrasonography—shrunken liver.
- Intracranial pressure, as detected by intracranial pressure monitoring, is raised.
- CSF is normal.

Complications

• Encephalopathy	• Pancreatitis
• Cerebral oedema	• Renal failure
• Respiratory failure	• Hypoglycaemia, hypokalaemia
• Bleeding, hypotension	• Hypocalcaemia, hypomagnesaemia
• Hypothermia	• Acid-base imbalance
• Infections	

Management

- General:
  - Monitor vital signs, hourly urine output, central venous pressure, renal functions and electrolytes.
  - Fluid and electrolytes therapy. In patients with normal intravascular volume fluids may be restricted to two-third of maintenance requirement. Hypokalaemia should be corrected.

- Calories are supplied as glucose (300 g/day) orally or by nasogastric tube or by infusion into a central vein.
- Ventilatory support for respiratory failure.
- Cefotaxime intravenously for reducing infections.
- Omeprazole or pantoprazole to prevent gastrointestinal bleed.
- Renal failure is treated with dialysis.
- Fresh frozen plasma if prothrombin time is more than 1.5 times the normal.
- Treatment of encephalopathy:
  - Protein-restricted diet (starting with 0.5 g/kg/day), antibiotic therapy (ampicillin, rifaximin, metronidazole or neomycin), lactulose, bowel washes, etc. (refer hepatic encephalopathy). Lactulose is catabolised by colonic bacterial flora to short-chain fatty acids (e.g. lactic acid and acetic acid) that lower the colonic pH. This reduction in pH favours the formation of the non-absorbable ammonium ion from ammonia, trapping ammonia in the colon and thereby reducing plasma ammonia concentrations.
  - Avoid sedatives if possible.
  - Restlessness and excitement are treated with smallest possible dose of diazepam or midazolam intravenously.
- Treatment of cerebral oedema:
  - Head elevation at 30° and elective ventilation in patients with grade 3 or 4 encephalopathy. The head should be in the midline because neck rotation or flexion may compromise jugular venous drainage and increase intracranial pressure.
  - Mannitol 20% (1 g/kg body weight) intravenously over half an hour. Dose may be repeated every 6 hours with serum osmolarity kept below 310 mOsm/L.
  - Controlled hyperventilation to maintain $PaCO_2$ between 30 and 35 mmHg (for short periods only).
  - Sodium thiopental can be used in controlling mannitol-resistant cerebral oedema. A bolus dose of 2–4 mg/kg over 15 minutes is followed by a slow intravenous infusion of 1–2 mg/kg/hour.
- Other measures:
  - Administration of vitamin K for prolonged prothrombin time may be of some benefit in patients with malnutrition, but usually is ineffective. Fresh frozen plasma is reserved for clinical evidence of bleeding or before invasive procedures.
  - N-acetylcysteine is recommended in all cases of acute liver failure with mild to moderate encephalopathy, particularly those with paracetamol toxicity.
  - Corticosteroids, exchange transfusion, plasmapheresis, charcoal haemoperfusion (molecular adsorbent recirculating system—MARS) and haemodialysis using special membranes have not been found to be helpful.
  - Liver transplantation.

Q. Give a brief account of subacute hepatic failure.

- Liver failure occurring between 4 and 24 weeks after onset of symptoms is called subacute liver failure. The diagnostic criteria for subacute liver failure are:
  - Persistent progressive jaundice for 4 weeks after its appearance in a patient with acute hepatitis.
  - Development of ascites 4 weeks after the appearance of jaundice.
  - Biochemical evidence of hepatocellular necrosis.
  - Submassive or bridging necrosis on liver biopsy.

Clinical Features

- Ascites is common.
- Hepatic encephalopathy occurs in 20–100% of the cases.
- Nausea, fever and abdominal pain.
- In contrast to acute liver failure cerebral oedema is uncommon while spontaneous bacterial peritonitis and renal failure are more common.
- Incidence of septicaemia and gastrointestinal haemorrhage is similar in acute and subacute liver failure.
- Hepatomegaly can occur in about half of the patients in contrast to shrunken liver seen in patients with acute failure.

Treatment

- Check ABCs of the patient and monitor blood glucose, electrolytes and renal functions.
- Role of glucose-insulin-potassium drip is controversial.
- The mortality ranges from 70 to 90% with renal failure accounting for about half of the deaths.
- Most of the survivors develop chronic liver disease.

Q. Describe Reye's syndrome.

- Usually in children and adolescents, rarely in adults.
- Follows an infectious illness like influenza or chickenpox.
- History of aspirin intake.
- Begins abruptly with vomiting and lethargy during the recovery period of a viral illness followed by acute encephalopathy with cerebral oedema.
- Severe fatty degeneration of the liver (causing elevations in ammonia levels and liver enzymes, but usually no jaundice).

Q. How do you classify chronic parenchymal liver diseases?
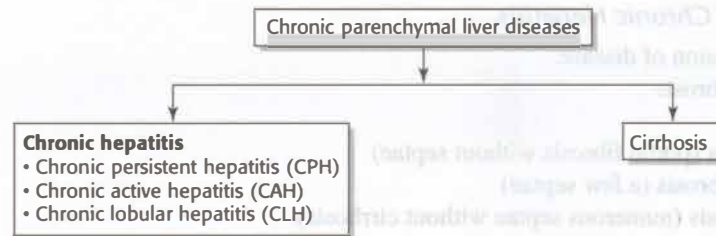
Q. Discuss the classification, aetiology, pathology, clinical features and management of chronic hepatitis.

- Chronic hepatitis is diagnosed when liver disease is present on clinical or other grounds for more than 6 months.

Old Classification

- Previously chronic hepatitis was classified into three types:
  - Milder forms were labelled as chronic persistent hepatitis (CPH) and chronic lobular hepatitis (CLH).
  - More severe forms were labelled as chronic active hepatitis (CAH).
- However these categories are not very helpful in prognosticating a patient with chronic liver disease.

New Classification

- In order to assess response to therapy and prognosis new classification system was developed.
- The new classification is based on combination of three factors:
  - Cause of chronic hepatitis
  - Histologic activity or grade
  - Degree of progression or stage.

Classification by Causes of Chronic Hepatitis

- Chronic hepatitis B
- Chronic hepatitis B plus hepatitis D
- Chronic hepatitis C
- Autoimmune hepatitis
- Drug-related chronic hepatitis
- Alcoholic hepatitis
- Non-alcoholic steatohepatitis
- Metabolic causes (primary biliary cirrhosis, sclerosing cholangitis, Wilson's disease, haemochromatosis, α1-antitrypsin deficiency)
- Cryptogenic chronic hepatitis

Classification by Grade of Chronic Hepatitis

- Grade indicates severity of liver disease and is based on the histopathological evidence of inflammatory and necrotic findings. Based on the severity of following factors, a severity score (mild, moderate or severe) is assigned (Knodell–Ishak score or histologic activity index):
  - Periportal necrosis including piecemeal necrosis and/or bridging necrosis
    - Piecemeal necrosis indicates swollen hepatocytes isolated in inflammatory cell infiltrate.
    - When piecemeal necrosis leads to septum formation linking portal tracts and central vein it is known as bridging necrosis.
  - Intralobular necrosis
  - Portal inflammation
  - Fibrosis (a part of staging of chronic hepatitis).

Classification by Stage of Chronic Hepatitis

- Indicates level of progression of disease.
- Based on the degree of fibrosis
  - Stage 0—no fibrosis
  - Stage 1—mild fibrosis (portal fibrosis without septae)
  - Stage 2—moderate fibrosis (a few septae)
  - Stage 3—severe fibrosis (numerous septae without cirrhosis)
  - Stage 4—cirrhosis.

Autoimmune Hepatitis (Lupoid)

- There are no features that are absolutely diagnostic and the existence of the condition can be established only by recognition of a constellation of compatible features and the exclusion of other diseases.

Clinical Features

- Seen in females during second or third decade.
- In majority, the onset is insidious with fatigue, anorexia and jaundice.
- In a few, the onset is acute like viral hepatitis but without the normal resolution.
- Fever, polyarthralgia, epistaxis and amenorrhoea.
- Jaundice (mild to moderate).
- Occasionally, maculopapular skin lesions, pleuritis, pericarditis and renal failure.
- Signs of chronic liver disease may be present—spider telangiectasia, hepatosplenomegaly.
- Associated conditions are migrating polyarthritis of large joints, lymphadenopathy, thyrotoxicosis, Hashimoto's thyroiditis, myxoedema, Coombs' positive haemolytic anaemia, pleurisy, transient pulmonary infiltrates, ulcerative colitis, glomerulonephritis and Sjogren's syndrome.
- Cholestasis is unusual and patients with pruritus, hyperpigmentation, xanthelasmas or disproportionately elevated serum alkaline phosphatase levels must be evaluated for other conditions.

Investigations

- Serum bilirubin is elevated by less than 6 mg%.
- Aminotransferases are elevated to more than 10 times during relapses.
- Hypoalbuminaemia and hyperglobulinaemia (IgG).
- Serum alkaline phosphatase is raised.
- Normal bilirubin and alkaline phosphatase with mild elevations in ALT in some patients.
- Prothrombin time is prolonged.
- Positive antinuclear antibodies (homogeneous pattern), antismooth muscle antibodies and antimitochondrial (type I hepatitis) antibodies.
- Anti-LKM1 (antiliver-kidney microsome type I) is present in a subtype of autoimmune hepatitis (type II; seen more frequently in children).
- HBsAg is negative.
- Liver biopsy shows aggressive hepatitis characterised by a chronic inflammatory cell infiltrate with or without cirrhosis. Interface hepatitis (e.g. centrilobular zone 3 necrosis) is typical. Other findings include bridging necrosis and fibrosis.
- Normal serum α1-antitrypsin and normal serum ceruloplasmin, iron and ferritin levels.

Prognosis

- Exacerbations and remissions are common.
- Progression to cirrhosis is limited in mild disease (e.g. piecemeal necrosis without bridging on biopsy).
- Some may progress rapidly to hepatic failure and death.
- Some develop cirrhosis and its complications.
- Hepatocellular carcinoma is uncommon.

Treatment

- Prednisolone 30–60 mg is given orally daily initially, then gradually taper as the liver function improves. Maintenance therapy to be continued for at least 2 years after LFT has become normal.
- Azathioprine 50–100 mg/day to be added if maintenance dose of prednisolone is more than 10 mg/day. In acute phase, prednisolone and azathioprine may be combined.
- Other immunosuppressive agents (mycophenolate mofetil, cyclosporine or tacrolimus) if no response.

Chronic Hepatitis B

- Chronic hepatitis B virus (HBV) infection affects 5% of the worldwide population and may lead to cirrhosis and hepatocellular carcinoma.
- HBV infection is considered as chronic when the surface antigen persists for more than 6 months.
- The risk of chronicity depends on the age at which the acute infection was contracted.
- If a child is infected at birth, acute infection is uncommon but chronic liver disease occurs in nearly 90% of cases.
- On the other hand, in immunocompetent adults, the incidence of acute hepatitis is high while chronic infection develops in only 1–2% of cases.
- Other conditions where incidence of chronic hepatitis B infection is high, are given in the box.

Conditions associated with chronic hepatitis B state

• Down's syndrome	• Polyarteritis nodosa
• Lepromatous leprosy	• Patients on chronic haemodialysis
• Leukaemias	• Needle using drug addicts
• Hodgkin's lymphoma	• HIV infection

- Chronic HBV infection has three major phases: immune-tolerant, immune-active and inactive carrier phases.
- Immune-tolerant phase:
  - Characterised by active viral replication in liver but little or no evidence of disease activity.
  - Immune system does not recognise the virus
  - Associated with high levels of HBV DNA in blood without liver inflammation.
  - Lasts for 10–30 years in perinatally acquired HBV but is shorter in those infected as children or adults.
- Immune-active phase (chronic hepatitis):
  - Most patients will eventually progress from the immune-tolerant phase to the immune-active phase.
  - Evidence of liver inflammation and elevated levels of liver enzymes.
  - Elevated HBV DNA levels (though levels are lower than in the immunotolerant phase).
  - Detectable levels of HBeAg.
  - Most often, the immune response results in decline in HBV DNA levels and HBeAg seroconversion can occur. Once HBV seroconversion occurs, there are three possible outcomes:
    - Inactive HBsAg carrier phase.
    - HBeAg negative chronic hepatitis B occurs in about 20% of persons after HBeAg seroconversion. They are HBeAg negative/anti-HBe positive with fluctuating levels of ALT and elevated HBV DNA levels.
    - Reversion back to HBeAg seropositivity (from 10 to 40% of persons, can develop one or more reversions back to HBeAg seropositivity, which may be associated with a flare of hepatitis that is usually subclinical).

Criteria for Chronic Hepatitis

- HBsAg positive >6 months
- Serum HBV DNA >20,000 IU/mL
- Persistent or intermittent elevation in ALT/AST levels
- Liver biopsy showing chronic hepatitis with moderate or severe necroinflammation

- Inactive HBsAg carrier phase:
  - Most people who have chronic HBV infection will eventually enter inactive carrier phase as they clear HBeAg and develop anti-HBe.
  - Accompanied by undetectable or low levels of HBV DNA, normalisation of ALT and reduced liver inflammation.
  - HBV DNA is still present in the blood during the inactive carrier phase, but at lower levels than during the immune-active phase.
  - Liver biopsy does not show any activity (grade).
  - Patients have a low-risk for hepatocellular carcinoma.
  - Liver abnormalities generally do not progress to more severe diseases.
  - Disease may be reactivated by severe immunosuppression.

Criteria for Inactive Carrier State

- HBsAg positive >6 months
- HBeAg negative, anti-HBe positive
- Serum HBV DNA <2000 IU/mL
- Persistently normal ALT/AST levels
- Liver biopsy confirms absence of significant hepatitis

- Persons who are infected as adults or adolescents generally become inactive carriers after they clear HBeAg. In contrast, persons who are infected at birth or in early childhood have a prolonged immune-tolerant phase and the disease continues to progress even after HBeAg disappears in some of these patients. Therefore lifelong monitoring is indicated.
- HBV genotype C infection (prevalent in India) poses an increased risk for cirrhosis and hepatocellular carcinoma.

Clinical Features

- The patient may be asymptomatic or has severe end-stage liver disease.
- Fatigue is a common symptom.
- Persistent or intermittent jaundice.
- Intermittent deepening of jaundice with recurrence of malaise and anorexia (episodes resembling acute hepatitis) may occur and may lead to progressive liver injury.
- Mild hepatomegaly.
- Complications of cirrhosis occur in end-stage liver disease.
- Extrahepatic manifestations include arthralgias, arthritis, vasculitis, glomerulonephritis and polyarthritis nodosa.
- Long-standing cases develop hepatocellular carcinoma.

Investigations

- Aminotransferase levels tend to be mildly elevated but may be as high as 1000 units. ALT (SGPT) tends to be more elevated as compared to AST (SGOT). Once cirrhosis develops AST exceeds ALT.
- The bilirubin level may be normal or elevated up to 10 mg/dL.
- Prolonged prothrombin time and hypoalbuminaemia occur in severe cases.
- Hyperglobulinaemia.
- Viral markers:
  - Positive HBsAg
  - Positive IgG anti-HBc, negative IgM anti-HBc
  - Positive HBe antigen or rarely, positive anti-HBe
  - Positive HBV DNA.

Treatment

- Criteria for treating chronic HBV (in both HBeAg negative and positive patients):
  - ALT level greater than two times normal.
  - HBV DNA >2000 IU/mL (>10,000 copies/mL).
  - Histological evidence of moderate to severe activity and/or fibrosis.
  - Positive test for HBeAg.
- In presence of cirrhosis (compensated or decompensated), oral drugs are recommended.

Interferon α-2b

- Response to interferon α-2b (defined as loss of HBeAg and HBV DNA) occurs in 30–40% of patients. Unfortunately, this therapy is associated with several side effects including flu-like symptoms, leucopenia, thrombocytopenia, depression, skin rash and others.
- Dose is 5 million units daily subcutaneously or 10 million units thrice a week for 4–6 months.
- Pegylated interferon-α can be used once a week.

Lamivudine

- The results are similar to those achieved by interferon therapy but this drug is better tolerated and is given orally.
- Dose is 100 mg once a day until HBeAg becomes negative.
- However, development of resistance is high and therefore, tenofovir and entecavir are recommended as the first-line oral agents.

Entecavir

- A cyclopentyl guanosine analogue that is a potent inhibitor of HBV DNA polymerase.

Tenofovir

- It is a cytosine nucleoside analogue with antiviral activity against both HBV and HIV.

Adefovir Dipivoxil

- A nucleotide reverse transcriptase inhibitor and may be useful in patients who develop resistance to lamivudine.

Telbivudine

- An L-nucleoside that is structurally related to lamivudine. May cause elevation of CPK.

Chronic Hepatitis C

- Chronicity is the hallmark of HCV infection. Approximately, 15–30% of patients with acute hepatitis C infection recover spontaneously whereas the remaining 70–85% patients develop chronic infection.
- Cirrhosis may develop in about 20% of cases after 20 years of exposure while hepatocellular carcinoma also develops in several patients (risk 1–4% per year in patients with cirrhosis).
- A number of factors can accelerate progression to advanced liver disease, most notably alcohol consumption, coinfection with HIV or HBV and older age at the time of infection.

Clinical Features

- Clinical features are similar to those with chronic hepatitis B. Fatigue is the most common symptom. Jaundice is rare.
- Chronic cases have prominent extrahepatic features that are mostly in the form of autoimmune and lymphoproliferative states. These include essential mixed cryoglobulinaemia, membranoproliferative glomerulonephritis, uveitis, peripheral neuropathy, non-Hodgkin's lymphoma, lichen planus, sicca syndrome and porphyria cutanea tarda.

Investigations

- Laboratory features are similar to those in patient with hepatitis B but aminotransferase levels tend to fluctuate more.
- Anti-HCV is positive in >95% cases.
- HCV-RNA is detectable in all patients, mostly continuously but occasionally and intermittently.
- Cryoglobulins are present in nearly 50% cases.

Treatment

- As acute infection with hepatitis A or B in those with underlying chronic HCV infection can result in high morbidity, hepatitis A and B vaccination should be performed in those who are sero negative for these viruses.
- Indications for antiviral treatment are:
  - Detectable HCV RNA with or without elevated ALT.
  - Findings of cirrhosis, fibrosis or moderate inflammation on biopsy (biopsy not mandatory).
- Previously untreated patients should receive a combination of pegylated interferon α-2a (or pegylated interferon α-2b) and ribavirin. Pegylated interferon is given once a week. Sustained virological response occurs in about 54% of patients.

For HCV-1, triple therapy with pegylated interferon, ribavirin and telaprevir or boceprevir (both are inhibitors of the HCV NS3 protease) has significantly increased cure rates to 70–75%. Triple therapy is also effective for patients who have previously failed dual therapy.

- Patients who have contraindications to ribavirin (pregnancy, end-stage renal failure, haemoglobinopathies, severe heart disease and uncontrolled hypertension) should be treated with interferon α-2a alone, preferably long-acting preparations of interferons, pegylated interferons. These long-acting preparations have been shown to be more effective as compared to the unmodified interferons.
- Liver transplant is the only available treatment option for patients with decompensated cirrhosis.

Chronic Hepatitis D (Plus Hepatitis B)

- Chronic hepatitis D may follow acute coinfection with hepatitis B but development of chronicity is not higher than that seen with hepatitis B infection.
- When hepatitis D infects a person with chronic hepatitis B, there is worsening of liver disease. Cirrhosis incidence is three times higher with hepatitis D infection than with HBV mono-infection.
- LKM3 antibodies are present in chronic hepatitis D infection.
- Management is supportive. Only pegylated interferon-α has proven antiviral activity against HDV as it leads to HDV clearance in about 25% of patients.

Q. Briefly discuss alcoholic liver disease.

- Chronic and excessive ingestion of alcohol can cause liver disease:
  - Fatty liver
  - Alcoholic hepatitis
  - Alcoholic cirrhosis (refer later).
- Threshold for developing alcoholic liver disease:
  - Intake of >60–80 g/day for 10 years in men
  - Intake of >20–40 g/day for 10 years in women.

Alcoholic Fatty Liver (Alcoholic Steatosis)

- Asymptomatic.
- Hepatomegaly.
- Occasionally, discomfort in right upper quadrant with tender hepatomegaly, nausea and jaundice.
- Progression to cirrhosis uncommon.
- Modest elevations of AST, ALT and GGTP.
- Occasionally, elevated bilirubin.
- Elevated triglycerides, cholesterol.
- Ultrasound shows fatty liver.
- Biopsy if done shows accumulation of fat in perivenular hepatocytes and later in entire hepatic lobule.
- Cessation of alcohol results in normalisation of pathological changes.

Alcoholic Hepatitis (Alcoholic Steatohepatitis)

- Many asymptomatic.
- Fever, rapid onset of jaundice, abdominal discomfort and proximal muscle wasting.
- Hepatomegaly.
- Features of chronic liver disease like spider angiomata, palmar erythema, chapped lips and gynaecomastia.
- In severe cases, portal hypertension, ascites and variceal bleed can occur without cirrhosis.
- Non hepatic manifestations of alcohol toxicity including polyneuropathy, cardiomyopathy and a history of chronic pancreatitis may be present.
- AST and ALT elevated two to seven fold, but usually <400 IU.
- AST:ALT ratio >2
- Elevated bilirubin.
- Mild increase in alkaline phosphatase.
- Reduced albumin.
- Prolonged prothrombin time.
- Leucocytosis, elevated C-reactive protein.

- Biopsy shows ballooning degeneration of hepatocytes with leucocyte infiltration. Mallory bodies often present.
- Potentially reversible but many progress to cirrhosis.

Prognosis

- High mortality in severe hepatitis.
- Poor prognostic factors include: Prothrombin time >5 seconds of control; anaemia; albumin <2.5 g/dL; bilirubin >8 mg/dL; renal failure; presence of ascites.
- Maddrey discriminant function >32 carries poor prognosis.
  - 4.6 × (patient's prothrombin time – control prothrombin time) + serum bilirubin.

Treatment

- Complete abstinence from alcohol.
- Nutritional support (>3000 kcal/day; multivitamins).
- Prednisolone may be tried in severe cases (discriminant function >32).
- Pentoxiphylline in severe cases (discriminant function >32).

Q. Discuss the aetiology, pathology, pathogenesis, classification, clinical features, investigations, complications and treatment of cirrhosis.

Q. Describe Laennec's cirrhosis and alcoholic cirrhosis.

Q. Enumerate the causes of gynaecomastia.

Q. Briefly explain Child-Pugh score or Child–Turcotte–Pugh score.

Causes

Aetiology of cirrhosis	
• Alcoholic cirrhosis	• Non-alcoholic fatty liver disease (NAFLD) Or Non-alcoholic steatohepatitis (NASH)
• Post-necrotic cirrhosis or post-viral cirrhosis	
• Hepatitis B	• Cardiac cirrhosis
• Hepatitis C	• Haemochromatosis
• Delta hepatitis (hepatitis D) + hepatitis B	• Wilson's disease
• Chronic autoimmune hepatitis	• α1-antitrypsin deficiency
• Drug-induced cirrhosis	• Glycogen storage diseases
• Methotrexate	• Galactosaemia
• Methyldopa, isoniazid	• Intestinal bypass surgery
• Sulphonamides	• Hepatic outflow tract obstruction
• Biliary cirrhosis	• Veno-occlusive disease
• Primary	• Cryptogenic (Idiopathic) cirrhosis
• Secondary	

Pathology and Pathogenesis

- Cirrhotic changes affect the whole liver, but not necessarily every lobule.
- Widespread necrosis of liver cells.
- Extensive fibrosis that distorts the hepatic architecture.
- Regenerative, nodular hyperplasia of the remaining surviving liver cells leads to regenerating nodules.
- Destruction and distortion of hepatic vasculature by fibrosis lead to obstruction of blood flow, which eventually leads to portal hypertension and its sequelae (gastro-oesophageal varices and splenomegaly).
- Ascites and hepatic encephalopathy result from both hepatocellular insufficiency and portal hypertension.
- Hepatocellular damage leads to jaundice, oedema, coagulopathy and a variety of metabolic abnormalities.
- Alcoholic cirrhosis:
  - Safe limits of alcohol are 200 g and 140 g of alcohol per week in males and females, respectively.
  - 10 g of alcohol equals 30 mL of whisky, 100 mL of wine and 250 mL of beer.
  - Occurrence of cirrhosis six times when alcohol intake is double the safety limit.

- Ingestion of 180 g of alcohol/day for 25 years increases the risk of developing cirrhosis 25 times.
- Hepatitis C infection is an important contributor for progression to cirrhosis.

Classification

- Micronodular cirrhosis (Laennec's cirrhosis)
  - Involvement of every lobule of whole liver.
  - Uniform, regular connective tissue septa.
  - Regenerating nodules of less than 3 mm diameter.
  - Most common cause is alcoholic cirrhosis.
- Macronodular cirrhosis
  - Liver surface is grossly distorted.
  - Connective tissue septa vary in thickness.
  - Regenerating nodules show marked differences in size.
  - Coarse, irregular nodules growing up to several centimetres.
  - Most common cause is chronic viral hepatitis.
- Mixed cirrhosis
  - Shows features of both micronodular and macronodular cirrhosis.

Note: This classification is rarely used at present as it is non-specific for aetiology, morphologic appearance of the liver may change as the liver disease progresses and serological markers available today are more specific than morphological appearance of the liver for determining the aetiology.

Clinical Features

Symptoms

- Low-grade fever.
- Weakness, fatigue and weight loss.
- Anorexia, nausea, vomiting and upper abdominal discomfort.
- Abdominal distension due to ascites and gas.
- Loss of libido.
- Menstrual irregularities like amenorrhoea and irregular menses.
- Haemorrhagic tendencies like easy bruising, purpura, epistaxis, menorrhagia and gastrointestinal bleeding.
- Haemorrhagic tendencies are due to underproduction of coagulation factors by the liver and thrombocytopenia resulting from hypersplenism.
- Symptoms of hepatic insufficiency (refer elsewhere).
- Symptoms of portal hypertension and its sequelae (refer elsewhere).

Signs

Signs of hepatocellular failure
- Jaundice
- Parotid enlargement
- Diminished body hair
- Spider naevi

- Palmar erythema
- Dupuytren's contracture
- Clubbing
- White nails

- Flapping tremors
- Gynaecomastia
- Testicular atrophy
- Ascites

Features dominant in male cirrhotics
- Diminished body hair
- Gynaecomastia
- Testicular atrophy

Features dominant in alcoholic cirrhosis
- Parotid enlargement
- Gynaecomastia
- Spider naevi
- Dupuytren's contractures (related to alcoholism)
- Liver enlarged, normal or small in size

Features dominant in female cirrhotics
- Menstrual irregularities
- Signs of virilisation
- Breast atrophy

- Jaundice
  - In the initial stages jaundice is fluctuating, but later the patient becomes chronically jaundiced.
  - Mechanisms of jaundice in cirrhosis are the following:
    - Failure of bilirubin metabolism (predominant mechanism)
    - Intrahepatic cholestasis
    - Haemolysis
- Diminished body hair
  - Seen mainly in males, who slowly loose the male hair distribution.
  - Alopecia affects mainly the face, axilla and chest.
  - Cause of alopecia is hyperoestrogenism.
  - Hyperoestrogenism is due to increased peripheral formation of oestrogen resulting from diminished hepatic clearance of the precursor, androstenedione.
  - Hyperoestrogenism is responsible for alopecia, gynaecomastia and testicular atrophy.
- Spider naevi
  - Syn: Spider telangiectasia; vascular spiders; spider angiomas; arterial spiders.
  - Thought to be due to arteriolar changes induced by hyperoestrogenism.
  - Seen in the territory drained by the superior vena cava (head and neck, upper limbs, front and back of upper chest).
  - Vary in size from 1–2 mm to 1–2 cm in diameter.
  - Seen as a central arteriole from which numerous small vessels radiate peripherally, resembling spider's legs. Compression of the central arteriole with a pinhead makes the whole spider disappear. Releasing compression shows filling from centre to periphery.

Conditions associated with spiders

- 2% of healthy individuals (≤3 in number)	- Alcoholic hepatitis
- Third trimester of pregnancy	- Rheumatoid arthritis
- Viral hepatitis	- Thyrotoxicosis

- Palmar erythema (liver palm)
  - Palmar erythema is due to increased peripheral blood flow. In cirrhosis, circulatory changes occur in the form of increased peripheral blood flow and decreased visceral blood flow, especially to the kidneys.
  - Seen as erythema of palm, especially thenar and hypothenar eminences.
  - May be seen on the sole. Also seen in hyperdynamic circulatory states and in some normal people.
- Dupuytren's contracture
  - Due to fibrosis of palmar aponeurosis.
  - Seen as a flexion contracture of the fingers, especially ring and little fingers, with loss of function.
  - Probably caused by local microvessel ischaemia and platelet and fibroblast-derived growth factors that promote fibrosis.
  - Other causes include diabetes mellitus and manual labour. An autosomal dominance inherited form is also seen.
- Clubbing and central cyanosis
  - Due to development of pulmonary arteriovenous shunts leading to hypoxaemia.
- Nail changes
  - White (Terry's) nails
    - Due to hypoalbuminaemia.
    - Nails become chalky white and brittle.
  - Muehrcke's nails
    - Pairs of transverse white lines that disappear on applying pressure.
    - Lines do not move with growth of nail.

- Flapping tremors
  - Seen in hepatic pre-coma (for further details, refer hepatic encephalopathy).
- Foetor hepaticus
  - A sweet and pungent smell in breath.
  - Caused by increased concentrations of dimethyl sulphide due to underlying severe portal-systemic shunting.
- Gynaecomastia
  - Seen in males (in females, there is atrophy of breasts).
  - Due to hyperoestrogenism.
  - Proliferation of male breast glandular tissue palpable as nodule (pseudogynaecomastia—accumulation of subareolar fat tissue without palpable nodule).

Causes of gynaecomastia	
- Physiological (ageing)	- Ketoconazole
- Cirrhosis of liver	- Oestrogens
- Spironolactone	- Klinefelter's syndrome
- Cimetidine	- Tumours of testes and lung
- Digoxin	- Hypogonadism

- Testicular atrophy
  - It is a consequence of hyperoestrogenic state.
- Ascites
  - Results from both hepatocellular insufficiency and portal hypertension (refer ascites).
- Parotid and lacrimal gland enlargement
  - Mechanism is not clear.
  - Seen more commonly in alcoholic cirrhosis.
- Skin pigmentation
  - Generalised hyperpigmentation of skin occurs due to increased melanin deposition.
- Anaemia
  - In cirrhosis anaemia can occur due to various reasons:
    - Acute and chronic blood loss from varices
    - Nutritional deficiency of vitamin B_{12} and folate
    - Hypersplenism
    - Direct bone marrow suppression by alcohol
    - Haemolysis due to the effect of hypercholesterolaemia on RBC membrane
- Hepatomegaly
  - In early stages of cirrhosis due to any cause, liver is enlarged, firm to hard, irregular and non-tender. More common in alcoholics.
  - In late stages, liver shrinks in size and becomes non-palpable. This is due to progressive hepatocyte destruction and fibrosis.
  - Other causes of enlarged liver with cirrhosis include primary biliary cirrhosis, primary sclerosing cholangitis, haemochromatosis and Wilson's disease.
- Portal hypertension, hepatic encephalopathy and renal failure
  - These are major complications of cirrhosis.
  - Symptoms and signs of portal hypertension and its sequelae (refer portal hypertension), hepatic encephalopathy (refer hepatic encephalopathy) and renal failure (refer hepatorenal syndrome) often coexist with cirrhosis.
- Other extrahepatic consequences
  - Pleural effusion (hepatic hydrothorax)
    - Defined as significant pleural effusion, usually greater than 500 mL, in a cirrhotic patient, without an underlying pulmonary or cardiac disease.
    - Most often develops on right side.
    - Ascites is also present in vast number of cases.
    - Proposed mechanisms include:
      - Hypoalbuminaemia—decreased colloid osmotic pressure
      - Leakage of ascitic fluid via diaphragmatic defects
      - Transdiaphragmatic migration of fluid via lymphatic channels

- Pleural fluid is transudative.
- Treatment involves control of ascites (refer later), transjugular intrahepatic portosystemic shunt, video-assisted thoracoscopy with pleurodesis, video-assisted thoracoscopy with repair of defects in the diaphragm and liver transplantation.
- Hepatopulmonary syndrome
  - Results in hypoxaemia through pulmonary microvascular vasodilatation and intrapulmonary arteriovenous shunting resulting in ventilation-perfusion mismatch. Probably occurs due to a defect in the synthesis and metabolism of pulmonary vasoactive substances by the impaired liver. This shunting predominates in middle and lower lung fields. Consequently, when a patient moves from a supine position to a standing position, blood flow to these fields increases and exacerbates the shunt and ensuing hypoxaemia (i.e. orthodeoxia).
  - Can occur even with mild liver disease.
  - Symptomatic patients frequently complain of insidious onset of progressive dyspnoea or orthodeoxia-platypnoea (platypnoea indicates dyspnoea accentuated by assumption of an upright position and relieved by assumption of a recumbent position).
  - Can also be present with cyanosis and clubbing.
  - Chest radiograph may show a bibasilar interstitial pattern that reflects the predominantly basal vascular dilatations.
  - Diagnosis by contrast-enhanced (microbubble) echocardiography, perfusion lung scan and pulmonary angiography.
  - Treatment by oxygen inhalation, coil embolisation (in localised shunts) and in severe cases, lung transplantation.
- Portopulmonary hypertension characterised by an elevated mean pulmonary artery pressure, increased pulmonary vascular resistance and normal wedge pressure in a setting of underlying portal hypertension. Dyspnoea on exertion is the most common symptom and other symptoms include orthopnoea, fatigue, syncope, chest pain and haemoptysis. Can lead to right heart failure.
- Cirrhotic cardiomyopathy
  - Constellation of features indicative of abnormal heart structure and function in patients with cirrhosis.
  - Include systolic and diastolic dysfunction, electrophysiological changes and macroscopic and microscopic structural changes.
  - Main clinical features include baseline increased cardiac output, attenuated systolic contraction or diastolic relaxation in response to physiologic, pharmacologic and surgical stress and prolonged QT interval.
- Hepatic osteodystrophy
  - Osteoporosis and osteomalacia

Severity of Liver Disease

- The Child–Pugh (CP) scoring classification, originally devised to risk-stratify patients undergoing shunt surgery is useful to assess liver disease severity in patients with established cirrhosis.

Child–Pugh Score or Child–Turcotte–Pugh Score

Parameter	Points		
	1	**2**	**3**
Encephalopathy (grade)	None	1–2	3–4
Ascites	None	Mild or controlled with diuretics	Moderate despite diuretics
Prolongation of prothrombin time (seconds)	<4	4–6	>6
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Serum bilirubin (mg/dL)	<2	2–3	>3

CP class A: Points 5–6; CP class B: 7–9; CP class C: >9 (range 5–15)

End Stage

- End stage of cirrhosis is characterised by:
  - Chronic jaundice.
  - Progressive, refractory ascites. Worsening of signs of portal hypertension.
  - Progressive renal dysfunction.
  - Most of them die in hepatic encephalopathy.

Complications

- Portal hypertension and its sequelae
- Ascites
- Spontaneous bacterial peritonitis
- Hepatic encephalopathy

- Hepatorenal syndrome
- Portal vein thrombosis
- Hepatocellular carcinoma
- Haemorrhagic manifestations
- Hepatopulmonary syndrome

Features of Poor Short-Term Prognosis in Cirrhosis

- Progressive jaundice (serum bilirubin more than 20 mg/dL)
- Rising serum creatinine
- Prolongation of prothrombin time more than 1.5 times of control
- Hyponatraemia of less than 120 mmol/L
- Hypoalbuminaemia of less than 2.5 g/dL
- Ascites responding poorly to therapy
- Encephalopathy not associated with an extensive collateral circulation

Investigations

- Complete blood picture
  - Anaemia.
  - Leucopenia and thrombocytopenia due to hypersplenism and bone marrow suppression by alcohol.
  - Acanthocytosis—spur-like projections on RBC.
- Liver function tests
  - Hyperbilirubinaemia of both conjugated and unconjugated types.
  - Serum proteins show A:G ratio reversal.
    - Serum albumin is decreased.
    - Serum globulin is increased.
    - Hypoalbuminaemia is due to impairment of hepatic protein synthesis.
    - Hyperglobulinaemia is due to non-specific stimulation of reticuloendothelial system.
  - Transaminases
    - AST (SGOT) is raised.
    - ALT (SGPT) is raised, but less than 300 units.
    - AST:ALT ratio is more than 2 in alcoholic cirrhosis (in contrast to viral hepatitis, where the ratio is less than 2).
  - Alkaline phosphatase may be mildly raised.
- Prothrombin time
  - Prolonged due to reduced synthesis of clotting proteins, especially the vitamin K-dependent factors.
- Hepatitis B and C markers .
- Blood ammonia estimation in cirrhosis is a reliable investigation, particularly in a situation where hepatic encephalopathy is suspected. The reasons for raised blood ammonia are:
  - Diminished hepatic clearance
  - Shunting of portal venous blood around the liver to systemic circulation.
- Respiratory alkalosis
  - Due to central hyperventilation
- Metabolic abnormalities
  - Glucose intolerance
  - Hyponatraemia
  - Hypokalaemia
  - Hypomagnesaemia
  - Hypophosphataemia.
- Ultrasonographic examination
  - Liver size small and coarse echotexture
  - Macronodules
  - Hypertrophied caudate lobe

- Splenic enlargement
- Portosystemic collaterals
- Ascites
- Ultrasound imaging every 6 months for hepatocellular carcinoma surveillance.
- Fibroscan to determine amount of fibrosis.
- Liver biopsy confirms the diagnosis of cirrhosis.
- Relevant investigations related to the specific aetiologies of cirrhosis in individual patients (serum α-foetoprotein, serum transferrin saturation level, serum ferritin, ceruloplasmin, α1-antitrypsin, antinuclear antibodies and antismooth muscle antibodies).
- Ascitic fluid examination, barium swallow for demonstration of varices, upper gastrointestinal scopy for delineation of varices.

Treatment

- Treatment of underlying causes
  - Removal of causative agents like drugs, alcohol, etc.
  - Oral antiviral therapy with entecavir or tenofovir in patients who are HBsAg positive irrespective of viral load.
  - Oral antiviral therapy with boceprevir or telaprevir for hepatitis C.
  - Immuno-suppression for autoimmune hepatitis.
  - Venesection for haemochromatosis.
  - Copper chelators or zinc for Wilson's disease
- High-protein diet—minimum 1 g/kg/day.
- 2000–3000 kcal/day.
- Diets enriched in branched-chain amino acids, in patients predisposed to hepatic encephalopathy.
- Multivitamin supplementation daily.
- Vaccination against hepatitis A and B viruses, influenza virus, and pneumococcus as early as possible, because the antigenic response becomes weaker as cirrhosis progresses.
- Penicillamine inhibits the formation of cross-links in collagen. Colchicine inhibits the assembly of collagen. However, none of them have shown any benefit.
- Specific treatment of complications—e.g. variceal bleeding, hepatic encephalopathy and ascites.

Q. **Write a short note on anatomy of the portal venous system. How do you define and classify portal hypertension?**

Q. **Discuss the aetiology, pathogenesis, clinical features, investigations and complications of portal hypertension.**

Anatomy of Portal Venous System
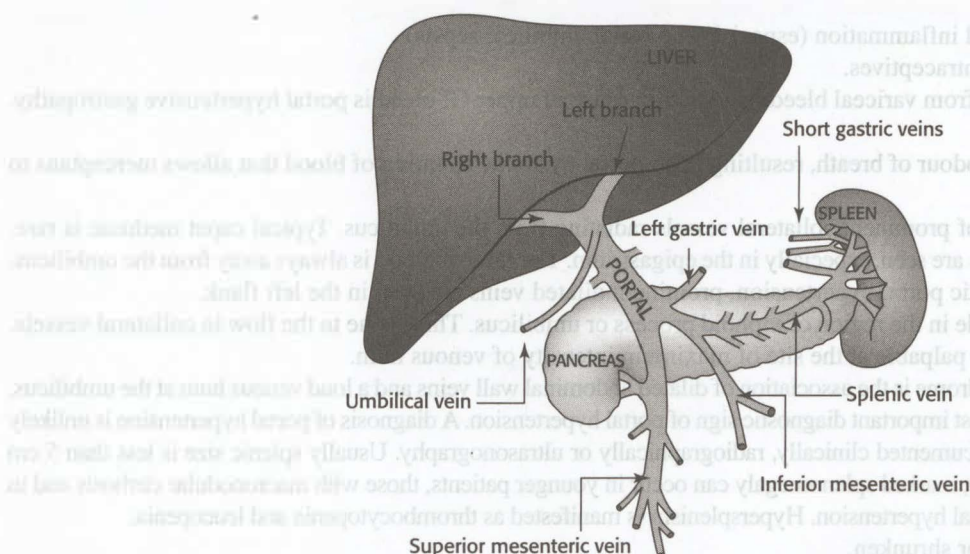
The anatomy of the portal venous system

Definition

- Portal hypertension is a condition characterised by prolonged elevation of portal venous pressure (more than 30 cm saline).
- Normal portal venous pressure is 10–15 cm saline or 7–10 mmHg.
- A better definition is hepatic venous pressure gradient (HVPG—difference in pressure between portal vein and hepatic vein) more than 5 mmHg. HVPG >10 mmHg defines significant portal hypertension.

Classification of Portal Hypertension

• **Pre-hepatic**	Portal vein thrombosis, splenic vein thrombosis
• **Intrahepatic**	
• Pre-sinusoidal	Non-cirrhotic portal fibrosis, schistosomiasis, primary biliary cirrhosis, sarcoidosis, tuberculosis, Wilson's disease, haemochromatosis
• Sinusoidal	Liver cirrhosis, acute viral and alcoholic hepatitis, acute fatty liver of pregnancy
• Post-sinusoidal	Veno-occlusion disease affecting central hepatic venules
• **Extrahepatic**	Hepatic vein thrombosis (Budd-Chiari disease), inferior vena caval occlusion, chronic right ventricular failure, chronic constrictive pericarditis, tricuspid insufficiency

- In prehepatic portal hypertension, the obstruction is in the main portal vein.
- In presinusoidal intrahepatic portal hypertension, the obstruction is usually in the portal tracts.

Pathogenesis

- Portal venous pressure is determined by:
  - Portal blood flow
  - Portal vascular resistance
- Increased portal vascular resistance is almost always the main factor producing portal hypertension, irrespective of its cause. Increased portal vascular resistance leads to:
  - Reduction in the flow of portal blood to the liver.
  - Development of collateral vessels allowing portal blood to bypass the liver and enter systemic circulation.
- Collateral vessel formation occurs particularly in the oesophagus, stomach, rectum, anterior abdominal wall and in the renal, lumbar, ovarian and testicular (spermatic) vasculature.
- With the development of collateral vessels, initially most of the portal blood and later almost all of the entire portal blood is shunted directly to the systemic circulation, bypassing the liver.

Clinical Features

- History and symptoms related to the aetiology of portal hypertension:
  - Alcoholism
  - Past history of hepatitis
  - Past history of abdominal inflammation (especially neonatal umbilical sepsis)
  - Prolonged use of oral contraceptives.
- Haematemesis and melaena from variceal bleeding. Another cause of upper GI bleed is portal hypertensive gastropathy.
- Stigmata of liver cell failure.
- Foetor hepaticus is a musty odour of breath, resulting from portal-systemic shunting of blood that allows mercaptans to pass directly to the lungs.
- Caput medusae—a number of prominent collateral vessels radiating from the umbilicus. Typical caput medusae is rare. Usually only one or two veins are seen, especially in the epigastrium. The flow of blood is always away from the umbilicus.
- In postsinusoidal, extrahepatic portal hypertension, prominent dilated veins are seen in the left flank.
- A venous hum may be audible in the region of xiphoid process or umbilicus. This is due to the flow in collateral vessels. Very rarely, a thrill might be palpable at the site of maximum intensity of venous hum.
- Cruveilhier–Baumgarten syndrome is the association of dilated abdominal wall veins and a loud venous hum at the umbilicus.
- Splenomegaly is the single most important diagnostic sign of portal hypertension. A diagnosis of portal hypertension is unlikely if splenomegaly cannot be documented clinically, radiographically or ultrasonography. Usually splenic size is less than 5 cm below costal margin. However, marked splenomegaly can occur in younger patients, those with macronodular cirrhosis and in presinusoidal intrahepatic portal hypertension. Hypersplenism is manifested as thrombocytopenia and leucopenia.
- Liver size may be enlarged or shrunken.
  - Small, contracted, fibrotic liver is associated with very high portal venous pressure.
  - Soft liver suggests extrahepatic portal vein obstruction.
  - Firm liver suggests cirrhosis and hence intrahepatic portal hypertension.

- Haemorrhoids may occur from dilation of rectal veins.
- Ascites occurs partly due to portal hypertension but is mainly due to liver cell failure. Portal hypertension determines the localisation of fluid to peritoneal cavity.

Complications of Portal Hypertension

• Ascites	• Portal hypertensive gastropathy
• Hepatic encephalopathy	• Hepatic hydrothorax
• Variceal haemorrhage	• Hepatopulmonary syndrome
• Spontaneous bacterial peritonitis	• Portopulmonary hypertension
• Hepatorenal syndrome	• Cirrhotic cardiomyopathy
• Hypersplenism	
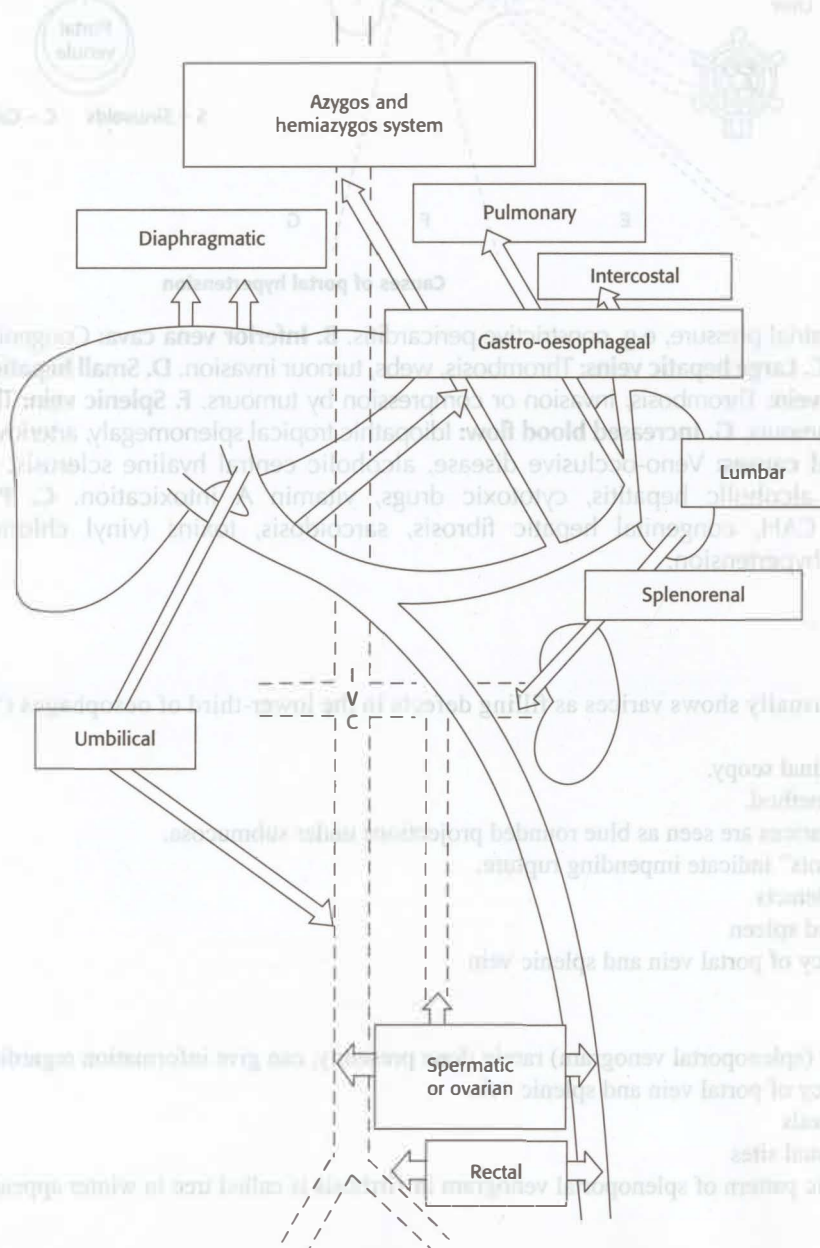
The sites of collateral circulation in the presence of intrahepatic portal vein obstruction

Causes of portal hypertension
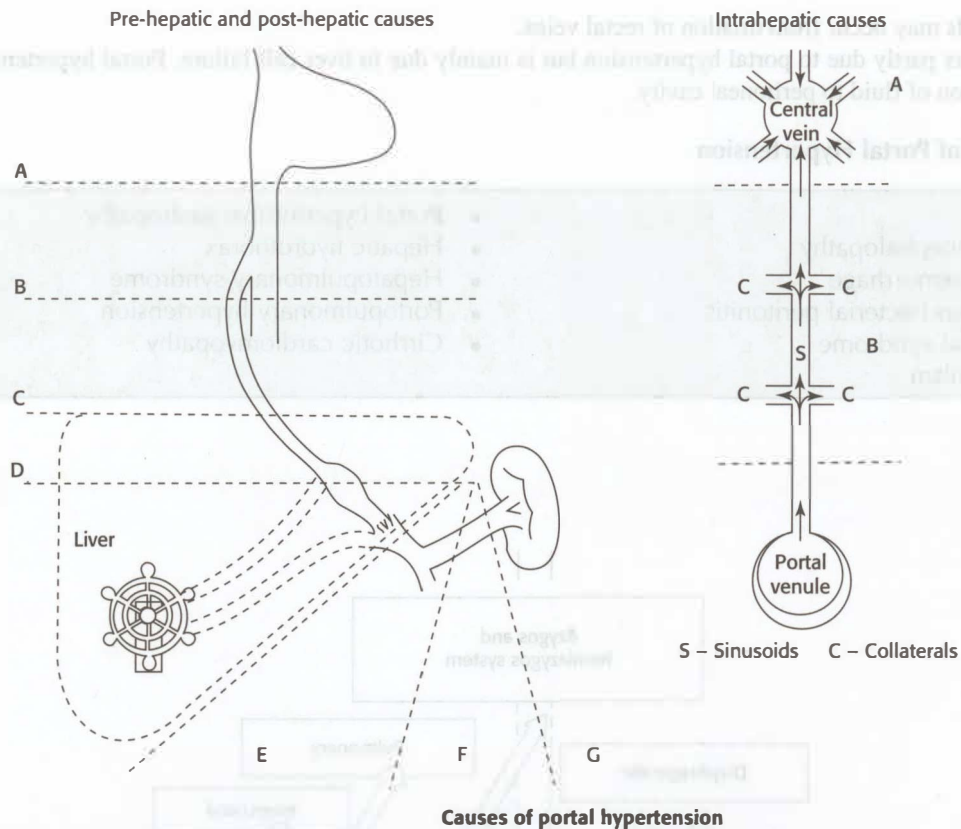
I. **A. Heart:** Rise in atrial pressure, e.g. constrictive pericarditis. **B. Inferior vena cava:** Congenital webs, tumour invasion, thrombosis. **C. Large hepatic veins:** Thrombosis, webs, tumour invasion. **D. Small hepatic veins:** Veno-occlusive disease. **E. Portal vein:** Thrombosis, invasion or compression by tumours. **F. Splenic vein:** Thrombosis, invasion or compression by tumours. **G. Increased blood flow:** Idiopathic tropical splenomegaly, arteriovenous fistulae.

II. **A. Post-sinusoidal causes:** Veno-occlusive disease, alcoholic central hyaline sclerosis. **B. Sinusoidal causes:** Cirrhosis, acute alcoholic hepatitis, cytotoxic drugs, vitamin A intoxication. **C. Pre-sinusoidal causes:** Schistosomiasis, CAH, congenital hepatic fibrosis, sarcoidosis, toxins (vinyl chloride, copper, arsenic), idiopathic portal hypertension.

Investigations

- Barium swallow usually shows varices as filling defects in the lower-third of oesophagus ("bag of worms appearance").
- Upper gastrointestinal scopy.
  - Most reliable method.
  - Oesophageal varices are seen as blue rounded projections under submucosa.
  - "Cherry red spots" indicate impending rupture.
- Ultrasonography detects
  - Size of liver and spleen
  - Size and patency of portal vein and splenic vein
  - Collaterals
  - Ascites.
- Portal venography (splenoportal venogram) rarely done presently, can give information regarding the following:
  - Size and patency of portal vein and splenic vein
  - Sites of collaterals
  - Varices at unusual sites
  - The intrahepatic pattern of splenoportal venogram in cirrhosis is called tree in winter appearance.

- Measurement of portal venous pressure by wedged hepatic venous pressure (WHVP) or transhepatic venous pressure:
  - Confirms portal hypertension.
  - Differentiates sinusoidal from pre-sinusoidal forms.
- Proctoscopy and barium enema for rectal and colonic varices.
- Liver function tests for liver diseases.

Complications

• Variceal bleeding	• Renal failure
• Hepatic encephalopathy	• Congestive gastropathy
• Ascites	• Hypersplenism

Treatment

- Non-selective β-blockers (propranolol and nadolol) produce vasodilatation of both splanchnic arterial bed and portal venous system along with reduced cardiac output. Also reduce recurrence of variceal bleed.
- Nitrates (nitroglycerine and isosorbide dinitrate) reduce venous return and post-sinusoidal resistance and are useful in combination with β-blockers in reducing risk of variceal bleed.
- β-blockers with or without nitrates are used for primary prophylaxis of variceal bleed.
- Treatment of underlying disease.

Q. Discuss the diagnosis and management of variceal bleeding.

- Commonest site of bleeding is oesophageal varices within 3–5 cm of the oesophagogastric junction.

Predisposing Factors

• Large varices	• Salicylates and other non-steroidal and anti-inflammatory drugs
• High portal venous pressure	• "Cherry red spots" on endoscopy
• Liver failure	

Clinical Features

- Painless, mild to massive haematemesis, with or without melaena.
- Associated signs vary from mild postural tachycardia to profound shock, depending on the extent of blood loss.
- Associated signs of liver cell failure, ascites and portal hypertension are usually present.

Diagnosis

- Fibreoptic endoscopy done within 8 hours of bleed usually shows the bleeding site and varices. This is essential to exclude other causes of bleeding.
- Ultrasonography to confirm the patency of portal vein.

Management

- Management is considered under five headings, viz. general measures, local measures, reduction of portal pressure, prevention of recurrent bleeding and primary prophylaxis (refer above).

General Measures

- Immediate hospitalisation and intensive care management.
- Monitoring vital signs, intake, output, fluid and electrolyte balance.
- Cirrhotics to be graded on Child–Pugh score immediately.
- Emergency blood transfusion (to maintain Hb around 8 g/dL) has the first priority. Saline infusions must be avoided as far as possible.
- Deficiency of clotting factors is corrected by fresh blood or fresh frozen plasma.
- Platelet transfusions raise platelet counts above 50,000/cmm.
- Injection of vitamin K intramuscularly.

- H₂ receptor antagonists (like cimetidine, ranitidine or famotidine) or proton-pump inhibitors (like pantoprazole or omeprazole) to prevent stress ulcers.
- Routine measures in cirrhotics to prevent hepatic encephalopathy (refer hepatic encephalopathy).
- Tense ascites is treated by careful paracentesis or spironolactone or amiloride.
- Antibiotic administration to prevent spontaneous bacterial peritonitis (norfloxacin or ciprofloxacin or cefotaxime or ceftriaxone).

Reduction of Portal Venous Pressure

- Vasopressin (pitressin)
  - Constricts the splanchnic arterioles and reduces portal pressure and portal blood flow.
  - 20 units of vasopressin in 100 mL of 5% glucose is given intravenously over 10 minutes; repeated if necessary 3–4 times at hourly intervals. It can also be given as an infusion: 0.4 units/minute until bleeding stops or for 24 hours and then 0.2 units/minute for a further 24 hours.
  - Abdominal colic, evacuation of bowels and facial pallor indicate that vasopressin is active. Absence of these suggest an inert preparation.
  - Adverse effects of vasopressin are the following:
    - Angina
    - Arrhythmias
    - Myocardial infarction
    - Mesenteric ischaemia
  - Sublingual or intravenous nitroglycerine (0.4 mg) is given to combat these adverse effects.
- Terlipressin
  - Terlipressin itself is not active, but vasopressin is released from it.
  - No systemic or cardiac side effects.
  - Given at a dose of 2 mg 6 hourly till bleeding stops and then 1 mg 6 hourly for a further 24 hours.
- Somatostatin and octreotide
  - Somatostatin and its synthetic analogue octreotide stop variceal bleed in more than 80% of cases.
  - Equivalent to vasopressin and endoscopic therapy.
  - Dose of somatostatin is 250 μg as bolus followed by 250 μg/hour for 2–5 days.
  - Dose of octreotide is 50 μg as bolus followed by 50 μg/hour for 2–5 days.

Local Measures

- Balloon tamponade
  - Sengstaken tube with three lumens.
  - Minnesota tube with four lumens.
    - These tubes have two balloons, oesophageal and gastric balloons.
    - The tube is introduced into the stomach, preferably through the mouth. The gastric balloon is inflated and pulled back into the cardia of the stomach. If bleeding does not stop, oesophageal balloon is inflated for additional tamponade.
    - If oesophageal balloon is used, it should be deflated for about 10 minutes every 3 hours to avoid oesophageal mucosal damage.
    - One lumen allows the aspiration of oesophageal contents and the other lumen of gastric contents.
    - Complications of balloon tamponade include necrosis and ulcerations of oesophagus, obstruction to pharynx and asphyxia.
- Endoscopic procedures
  - These include endoscopic sclerotherapy (stops bleeding in 80–90% of cases) and endoscopic variceal band ligation (EVBL). EVBL is the treatment of choice.
- Other procedures
  - If the patient does not respond to these measures, transjugular intrahepatic portosystemic shunt (TIPSS) is helpful in most patients.
  - Surgical procedures should be considered for continued or recurrent haemorrhage. The options include portosystemic shunting and oesophageal staple transaction.

Treatment of Acute Variceal Bleed

General management	• Secure intravenous access
	• Monitor vital signs, intake, output, fluid and electrolyte balance.
	• Resuscitation but limit transfusion to haemoglobin level of 7–8 g/dL
	• H$_2$-antagonists or proton-pump inhibitors
Vasoconstrictor	• Vasopressin or octreotide or somatostatin or terlipressin
Antibiotic prophylaxis	• Cefotaxime or norfloxacin
Endoscopic therapy	• Endoscopic variceal ligation
	• Endoscopic sclerotherapy
Others	• Balloon tamponade using Sengstaken tube or Minnesota tube
	• Transjugular intrahepatic portosystemic shunt

Prevention of Recurrent Bleeding (Secondary Prophylaxis)

- Bleeding reoccurs in approximately 65% of patients within 1 year after initial bleed.
- Medical treatment
  - It consists of non-selective β-blockers (propranolol 80–160 mg/day) in combination with nitrates.
- Endoscopic sclerotherapy
  - Endoscopic sclerotherapy may be considered if the patient cannot tolerate medical therapy. However, its efficacy is inferior to medical treatment.
  - Commonly used sclerosants are the following:
    - Ethanolamine oleate
    - Sodium morrhuate
    - Absolute alcohol
    - Sodium tetradecyl sulphate
  - Injections are repeated for every 2 weeks thereafter until the varices are obliterated.

Complications of Sclerotherapy

• 1% mortality	• Oesophageal reflux
• Abdominal pain, fever and dysphagia	• Pulmonary complications like chest pain, pleural effusion, mediastinitis and aspiration pneumonia
• Reappearance of varices	
• Oesophageal ulceration and perforation	• Acute respiratory failure
• Stricture formation	• Spinal cord paralysis due to anterior spinal artery occlusion

- EVBL
  - EVBL alone or in combination with β-blockers is the therapy of choice in these patients.
- TIPSS
  - TIPSS is more effective than EVBL for the prevention of recurrent variceal bleed but the incidence of hepatic encephalopathy is higher with this mode of therapy.
- Portal–systemic shunt surgery
  - Reserved for patients in whom medical therapy, EVBL and sclerotherapy have not been successful.
  - Done only in those with good liver function (Child–Pugh A and B).
  - There are two types of portal systemic shunts:
    1. Non-selective shunts that decompress the entire portal venous system
       - End-to-side portocaval shunt
       - Side-to-side portocaval shunt
       - Proximal splenorenal anastomosis
       - Mesocaval shunt

2. Selective shunts decompress only the varices while maintaining blood flow to liver itself.
    - Distal splenorenal shunt (Warren shunt)
- Non-selective shunts have a high degree of post-operative hepatic encephalopathy.
- Selective shunt (distal splenorenal shunt) induces much less encephalopathy.
- Complications of portosystemic shunts:
    - Operative mortality of 5%
    - Shunt closure
    - Hepatic encephalopathy occurs transiently in post-operative periods
    - Chronic hepatic encephalopathy occurs in 20–40% of cases, especially in non-selective shunts. Encephalopathy following surgery is due to two mechanisms:
        1. Reduction in portal pressure and hepatic blood flow leading to deterioration of hepatocellular function.
        2. Encephalopathy inducing toxic substances carried by the portal system are normally metabolised by the liver. Following shunt, these substances bypass the liver and enter systemic circulation, thereby reaching the brain.
    - Post-operative jaundice due to deterioration of hepatocellular function
    - Chronic ankle oedema
    - Personality deterioration

Primary Prophylaxis

- β-blockers
- Nitrates
- EVBL if patients cannot tolerate β-blockers
- Endoscopic sclerotherapy and shunt procedures not recommended for primary prophylaxis

Q. Name the drugs that are used in the reduction of portal venous pressure.

• Vasopressin	• Somatostatin	• Propranolol	• Nitroglycerine
• Terlipressin	• Octreotide	• Nadolol	

Q. Define hepatic (portosystemic) encephalopathy. Discuss the aetiopathogenesis, clinical features, investigations and treatment of hepatic encephalopathy.

Definition

- Hepatic (portosystemic) encephalopathy is a neuropsychiatric syndrome characterised by the following:
    - Disturbances in consciousness and behaviour
    - Personality changes
    - Fluctuating neurologic signs
    - Asterixis or "flapping tremor"
    - Distinctive electroencephalographic changes
    - Hepatic encephalopathy may be acute and reversible, or chronic and progressive.

Aetiology and Pathogenesis

- Hepatic encephalopathy is due to a biochemical disturbance of brain function resulting from various toxic substances reaching the brain. These toxic substances are normally derived from the intestine and carried by portal circulation to the liver, where they are detoxified. Hence, they normally do not enter the systemic circulation or reach brain.
- In hepatic encephalopathy, three factors operate that permit these toxic substances to reach brain.
    - Severe hepatocellular dysfunction leading to defective detoxification.
    - Intrahepatic and extrahepatic shunting (collaterals) of portal venous blood into systemic circulation, allowing toxins to enter the systemic circulation. Here, the liver is "bypassed".
    - Increased permeability of the blood–brain barrier, allowing the toxins to enter the brain.

Toxic Substances

• Ammonia—most important	• Octopamine
• γ-aminobutyric acid (GABA)	• Amino acids
• Mercaptans derived from methionine	• Phenol
• Short-chain fatty acids	

Precipitating Factors

• Gastrointestinal bleeding	• Acute infections
• Increased dietary protein	• Uraemia
• Large volume paracentesis	• Sedatives
• Hypokalaemia, hyponatraemia	• Constipation
• Vomiting and diarrhoea	• Viral/alcoholic hepatitis
• Overzealous use of diuretics	• Surgical shunts

- Gastrointestinal bleeding leads to an increase in the production of ammonia and other nitrogenous substances in the gut, which are absorbed and carried to brain.
- Increased dietary protein is acted upon by the intestinal bacteria to produce excess nitrogenous substances.
- Diuretics, paracentesis and vomiting precipitate hepatic encephalopathy by electrolyte imbalance, particularly hypokalaemic alkalosis.
- Mechanism of encephalopathy in surgical portosystemic shunts is discussed under "shunt surgery".

Clinical Features

- Disturbances in consciousness and behaviour
  - Hypersomnia is the earliest feature, which progresses to inversion of sleep rhythm.
  - Reduction of spontaneous movements, fixed stare, apathy, slowness and brevity of response.
  - Later, confusion, disorientation, drowsiness and eventually coma develop.
  - Convulsions occur rarely.
- Personality changes
  - Childishness, irritability and loss of concern for family
  - Slight impairment of organic mental function to gross confusion
  - Defaecating and micturating in inappropriate places
- Fluctuating neurological signs
  - Slurred speech
  - Constructional apraxia
  - Hypertonia
  - Hyperreflexia
  - Bilateral extensor plantar response
  - Hyperventilation and hyperpyrexia
- Asterixis or flapping tremor
  - Most characteristic neurologic abnormality.
  - Due to impairment of flow of joint position sense and other afferent information to the brainstem reticular formation, resulting in lapses of postures (negative myoclonus).
  - It is best demonstrated by having the patient extend the arms and dorsiflex the hands. It is manifested as the rapid flexion extension movements at metacarpophalangeal and wrist joints, accompanied by lateral movement of digits.
  - Asterixis can also be demonstrated on head and trunk.
  - Other conditions associated with flapping tremor are the following:
    - Uraemia
    - Respiratory failure
    - Severe heart failure

Cerebral disturbance

Portal collateral vein

Hepatic vein

Hepatocellular disease

Sources of nitrogen
- Food protein
- Ingested blood
- Drugs
- Bacterial action

Portal vein

Intestine
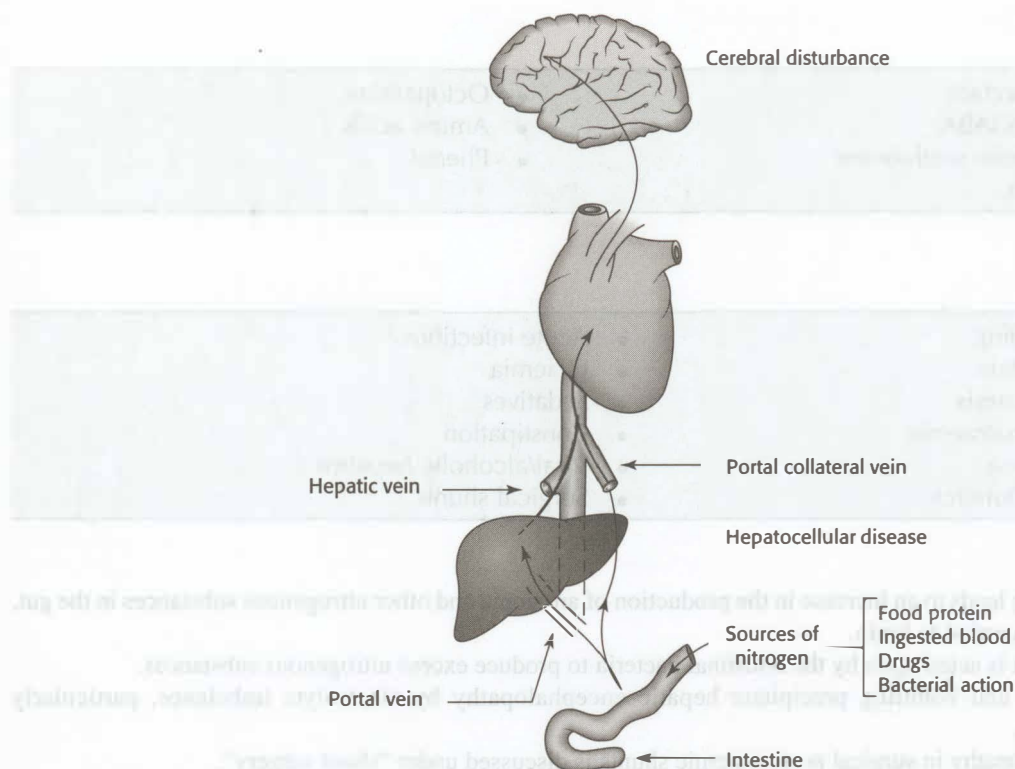
The mechanism of portosystemic encephalopathy

Investigations

- Blood ammonia levels are raised (upper limit of normal is 0.8–1 µg/mL).
- Electroencephalogram shows delta waves—the characteristic, symmetric, high voltage, slow wave (2–5 per second) waves.
- Cerebrospinal fluid
  - Normal proteins
  - Increased glutamine
  - Normal cell count
- Visual evoked potential abnormalities may be present in incipient stages.
- Liver functions.

Treatment

- Treatment or removal of the precipitating causes.
- Maintain calories (glucose 300 g/day).
- Correct electrolyte imbalance.
- Restricting proteins in diet is not recommended at present. Administer 1.0–1.5 g/kg of proteins daily.
- In gastrointestinal bleeding, Ryles tube aspiration and bowel washes are employed to remove the blood and blood products. This reduces the nitrogen production in the gut.
- Oral neomycin 0.5–1 g 6 hourly to sterilise the gut. This reduces the intestinal ammonia production by bacteria. Main side effects of neomycin are nephrotoxicity and ototoxicity. Therefore, at present, neomycin is not used commonly. Alternatives include metronidazole and rifaximin (a non-absorbable derivative of rifampicin).
- Lactulose syrup 15–30 mL three times orally per day. Dose is increased gradually till there are 2–3 loose stools per day.
  - Metabolism of lactulose by colonic bacteria results in an acidic pH in the intestine, which favours conversion of ammonia to ammonium, which is poorly absorbed.
  - Lactulose diminishes ammonia production by its direct effect on bacterial metabolism.
- Lactitol has a similar action, more palatable and is a better option than lactulose.
- Intravenous mannitol to reduce the spontaneous cerebral oedema (controversial).

- Levodopa, bromocriptine, keto-analogues of essential amino acids and branched chain amino acids, L-ornithine-L-aspartate (stable salt of ornithine and aspartic acid) (controversial).
- Haemoperfusion to remove toxic substances.
- Hepatic transplantation is the ultimate cure.

Q. Write a short note on hepatorenal syndrome.

- Hepatorenal syndrome is renal failure with normal tubular function in a patient with chronic liver disease in the absence of an identifiable cause of renal failure.
- Kidneys are histologically normal and the renal failure is functional. Such kidneys have been successfully transplanted and function well.
- Pathogenesis
  - Splanchnic vasodilatation that causes a reduction in effective arterial blood volume and a decrease in mean arterial pressure.
  - Activation of sympathetic nervous system and renin–angiotensin–aldosterone system that causes renal vasoconstriction.
  - Impairment of cardiac function due to development of cirrhotic cardiomyopathy.
  - Increased synthesis of several vasoactive mediators that may affect renal blood flow.
- Precipitating factors
  - Gastrointestinal bleeding
  - Sepsis including spontaneous bacterial peritonitis
  - Diarrhoea
  - Diuretic therapy
  - Aggressive paracentesis
- Two types of hepatorenal syndrome:
  - Type 1 hepatorenal syndrome is defined as a rapid deterioration of renal function indicated by a two fold increase of serum creatinine to values above 2.5 mg/dL or a decrease of creatinine clearance to values below 20 mL/minute in less than 2 weeks. It is usually precipitated by spontaneous bacterial peritonitis. The median survival duration is less than 2 weeks without treatment and almost all patients die within 10 weeks after the onset of renal failure.
  - Patients with type 2 hepatorenal syndrome have moderately increased serum creatinine (>1.5 mg/dL) that remain stable over a longer period and ascites that generally is resistant to diuretics. The median survival duration in these patients is 3–6 months.
- Clinical features
  - Occurs in advanced cirrhosis, almost always with ascites.
    - Anorexia, weakness and fatigue
    - Refractory ascites
    - Oliguria, nausea, vomiting and thirst
    - Terminally, coma deepens and hypotension ensues
- Investigations
  - Urinalysis is normal.
  - Urea and creatinine levels are high. Serum sodium is less than 120 mEq/L.
  - Urine sodium excretion is less than 10 mEq/day.
  - Urine: plasma osmolality ratio is more than 1.5.
- Diagnostic criteria.

All of the following must be present:
- Cirrhosis with ascites
- Serum creatinine >1.5 mg/dL
- No improvement of serum creatinine (decrease to a level of 1.5 mg/dL or less) after at least 2 days of diuretic withdrawal and volume expansion with albumin (1 g/kg body weight/day up to a maximum of 100 g/day)
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhaematuria (>50 red blood cells per high power field), and/or abnormal renal ultrasonography

- Treatment
  - Prevention includes avoiding overdosage of diuretics, slow treatment of ascites and early recognition of electrolyte imbalance, haemorrhage or infection.
  - Hypovolaemia to be treated by intravenous plasma protein solution or salt-poor albumin.
  - Screening and treatment of infection including SBP.
  - The only effective medical therapy available is the use of vasoconstrictors. Vasopressin analogues (terlipressin) and α-adrenergic agonists (norepinephrine and midodrine plus octreotide) along with infusion of albumin have been used with encouraging results.
  - TIPSS if vasoconstrictors fail.
  - Protein restriction.
  - Dialysis.
  - Treatment of choice is liver transplant.

Q. Discuss the pathogenesis and management of ascites and refractory ascites in cirrhosis.

Pathogenesis

- Ascites represents a state of total body sodium and water excess.
- Ascites in cirrhosis results from a combination of the following:
  - Liver failure
  - Portal hypertension.

Mechanisms Involved in Pathogenesis

- Renal mechanism
  - Liver failure leads to redistribution of blood flow, resulting in a decrease in renal blood flow. This in turn causes a reduction in the glomerular filtration rate and excessive reabsorption of salt and water by the renal tubules. This results in salt and water retention and hence, ascites.
- Secondary hyperaldosteronism
  - Decreased renal blood flow leads to increased release of renin, which stimulates the angiotensin system, that in turn leads to secondary hyperaldosteronism. The secondary hyperaldosteronism results in salt and water retention. Failure of liver to metabolise aldosterone intensifies secondary hyperaldosteronism.
- Vasopressin
  - Failure of liver to metabolise vasopressin reduces renal water clearance that results in fluid retention.
- Increased capillary hydrostatic pressure
  - Portal hypertension raises the hydrostatic pressure within the splanchnic capillary bed. This results in extravasation of fluid from plasma into the peritoneal cavity.
- Reduced plasma oncotic pressure
  - Hypoalbuminaemia results in a reduction of plasma oncotic pressure. This again results in an extravasation of fluid (ascites and oedema).
- Hepatic lymph
  - Hepatic lymph oozes freely from the surface of cirrhotic liver into the peritoneal cavity. This adds to the development of ascites.
  - So, portal hypertension and lymphatic ooze predispose to localisation of fluid within the peritoneal cavity.

Ascitic Fluid in Cirrhosis

- Appearance—clear, straw coloured or light green
- Specific gravity—less than 1.016
- Protein—less than 2.5 g/dL
- Total cell count—normal (<250/μL)
- SAAG* ≥1.1 g/dL
- Differential cell count—majority of the cells are mesothelial cells and lymphocytes
- Gram's stain—negative
- Culture—negative
- Malignant cells—absent

*SAAG—Serum ascites albumin gradient, i.e. the difference between serum albumin and ascitic fluid albumin. It is a better test rather than simple estimation of protein in the ascitic fluid

- Total ascitic fluid protein concentration <1.5 g/dL indicates an increased risk of spontaneous bacterial peritonitis.

Management

- The goal of the therapy is the loss of no more than 1.0 kg body weight daily if both ascites and peripheral oedema are present and no more than 0.5 kg body weight daily in patients with ascites alone.
    - General measures.
        - Hospitalisation if ascites is massive
        - Estimation of daily body weight
        - Strict intake and output recording
        - Estimation of abdominal girth daily
        - Urinary electrolyte determination
        - Estimation of serum electrolytes and renal function tests twice a week
    - Bed rest induces diuresis because renal blood flow increases in the horizontal position.
    - Strict salt-free diet initially, but later allowing 4–6 g of salt (equivalent to a no added-salt diet with avoidance of pre-prepared meals).
    - Fluid restriction to 1000–1500 mL/day if there is hyponatraemia. Routine restriction of fluid intake not recommended.
    - Diuretics
        - Diuretics are introduced in a step-wise manner.
        - As there is secondary hyperaldosteronism, one of the aldosterone antagonists (potassium-sparing diuretics) is preferred—e.g. spironolactone, triamterene, amiloride.
        - Spironolactone is the drug of choice. It is started at a low dose of 25 mg QID and gradually stepped up every week to a maximum of 400 mg/day.
        - When a large dose of spironolactone has failed, add one of the potent diuretics (e.g. furosemide, torsemide, a thiazide, ethacrynic acid). Usual combination is spironolactone plus furosemide or torsemide.
        - Diuretic dosage is adjusted to achieve a rate of weight loss of no greater than 0.5 kg/day in patients without peripheral oedema and 1 kg/day in those with peripheral oedema (to prevent diuretic-induced renal failure and/or hyponatraemia).
        - Stop all diuretics if severe hyponatraemia (sodium <120 mEq/L), progressive renal failure or worsening hepatic encephalopathy develops.

Treatment of Refractory Ascites

- Failure to respond to dietary and diuretic regime indicates refractory ascites. Such cases are managed on the following lines:
    1. Intravenous salt-poor albumin, 25 g in 3 hours.
    2. Large-volume paracentesis
        - Indications of large-volume paracentesis are the following:
            - Cardiorespiratory distress due to gross ascites
            - Impending rupture of a hernia
            - Refractory ascites
        - Remove 3–5 L of fluid over 1–2 hours. Salt-free albumin (8 g per litre of ascitic fluid removed) required if volume is more than 4–5 litres. Dextran-70 may be used if albumin is not available. Strict monitoring is required.
        - Can produce circulatory dysfunction due to a reduction of effective blood volume, a condition known as post-paracentesis circulatory dysfunction.
    3. TIPSS is applied in patients with refractory ascites who may require a transplant. Complications include hepatic encephalopathy and shunt thrombosis.
    4. LeVeen shunt. It is a peritoneovenous shunt that allows the peritoneal fluid to drain directly into the internal jugular vein. Should be considered in patients with refractory ascites who are not candidates for paracentesis, transplant or TIPSS.
        - Common complications of LeVeen shunt are:
            - Infection
            - Superior vena caval thrombosis
            - Pulmonary oedema
            - Bleeding from oesophageal varices
            - Disseminated intravascular coagulation
    5. Side-to-side portocaval shunt.
    6. Liver transplantation.

Q. Briefly explain spontaneous bacterial peritonitis (SBP).

- Patients with cirrhosis and ascites are highly susceptible to infection of ascitic fluid (SBP).
- Definition
  - Spontaneous bacterial peritonitis is defined as infected ascitic fluid in the absence of a recognisable secondary cause of peritonitis.
- Clinical features
  - May present as an abrupt deterioration or hepatic encephalopathy in a cirrhotic patient with ascites.
  - Usually, presentation is abrupt onset of fever with chills, abdominal pain and rebound abdominal tenderness.
  - A diagnostic paracentesis should be performed in patients with gastrointestinal bleeding, shock, fever, worsening liver and/or renal function and hepatic encephalopathy as incidence of SBP is high in these conditions.
- Investigations
  - Blood leucocytosis
  - Ascitic fluid characteristics:
    - Cloudy fluid
    - Leucocyte count is more than 500/mm^3 or polymorphs are more than 250/mm^3.
    - pH less than 7.3.
    - Culture is positive. *E. coli* is the most common organism. Others include streptococci and enterococci.
- Treatment
  - Cefotaxime 2 g IV 8 hourly for 5 days.
  - Alternative therapy is amoxicillin/clavulanate (1.2 g IV 8 hourly followed by 625 mg orally), ciprofloxacin (200 mg IV 12 hourly followed by 500 mg BID orally) or ofloxacin (400 mg twice daily) in patients without shock or hepatic encephalopathy. However, quinolones should not be given if patient is on norfloxacin for prophylaxis.
  - Antibiotic therapy and albumin (1.5 g/kg body weight within 6 hours of detection and 1 g/kg on day 3) reduces risk of type 1 hepatorenal syndrome, particularly if creatinine >1 mg/dL or bilirubin >4 mg/dL.
- Prophylaxis
  - High-risk patient populations where prophylaxis is indicated are:
    - Patients with acute gastrointestinal haemorrhage (antibiotic prophylaxis also decreases rate of rebleeding).
    - Patients with low total protein content <1.5 g/dL in ascitic fluid and no prior history of SBP (primary prophylaxis).
    - Patients with a previous history of SBP (secondary prophylaxis; recurrence in as many as 70% cases in first year).
  - In patients with upper GI haemorrhage, cefotaxime or norfloxacin (400 mg BID for 7 days).
  - In patients with low ascitic protein content or previous episode of spontaneous bacterial peritonitis, long-term norfloxacin (400 mg/day) for prophylaxis. Alternative but less effective drugs include cotrimoxazole (800 mg sulphamethoxazole +160 mg trimethoprim once a day) or ciprofloxacin (750 mg once a week).

Q. Discuss the definition, mechanism, causes, clinical features and differential diagnosis of ascites.

Q. What is Puddle sign?

Definition

- Ascites is defined as an accumulation of excess fluid within the peritoneal cavity.

Mechanisms

- For mechanisms of ascites in cirrhosis and portal hypertension, refer "ascites due to cirrhosis".
- Inflammation of peritoneum leads to increased capillary permeability and exudation of fluid into the peritoneal cavity. The same mechanism is responsible for diminished reabsorption of fluid. Both these factors favour the development of ascites in bacterial peritonitis and tuberculous peritonitis.
- Venous obstruction can lead to transudation of fluid into peritoneal cavity, e.g. inferior vena caval (IVC) obstruction.
- Lymphatic obstruction can lead to chylous ascites. Involvement of mesenteric lymph nodes, thoracic duct and abdominal lymphatic ducts can result in leakage of chyle into peritoneal cavity.
- Rupture of a viscus can result in outpouring of blood, cystic fluid or contaminated material, favouring ascites, e.g. pancreatitis.

Causes

Transudates	Exudates
• Cirrhosis and portal hypertension	• Tuberculous peritonitis
• Congestive cardiac failure	• Malignant peritonitis
• Nephrotic syndrome	• Bacterial peritonitis
• Constrictive pericarditis	• Pancreatic ascites
• Beriberi	**Miscellaneous (exudative/transudative)**
• Hypoproteinaemia of any cause	• Meigs' syndrome
• Inferior vena caval (IVC) obstruction	• Chylous ascites
	• Budd–Chiari syndrome

Clinical Features

Symptoms

- Abdominal distension.
- Bloated feeling of abdomen.
- Dyspnoea and orthopnoea due to elevation of diaphragm.
- Indigestion and heart burns due to gastro-oesophageal reflux resulting from increased intra-abdominal pressure.

Signs

- Abdominal distension and fullness of flanks.
- Skin over the abdominal wall may become stretched and shiny with striae albicans.
- Umbilicus may be flat or everted.
- Divarication of recti and herniae.
- Prominence of hypogastrium in the erect posture.
- Abdominal wall may show distended veins of two types. Veins radiating out from the umbilicus with flow away from the umbilicus represent collaterals due to portal hypertension (caput medusae). Prominent veins in the flanks with flow from below upwards represent the IVC collaterals, resulting from compression of IVC by severe ascites.
- In moderate ascites the dullness is confined to only flanks. With larger amounts the flanks and hypogastric areas are dull (horseshoe-shaped dullness). The epigastrium and umbilical regions remain resonant due to floating intestines. In massive ascites the whole of the abdomen is dull except for a small area over the umbilical region.
- Shifting dullness elicitation requires a minimum of 1000 mL of fluid.
- Fluid thrill is elicitable in tense ascites.
- Paraumbilical zone of dullness is detected with smaller amounts of fluid. The patient is put in knee elbow position and paraumbilical region percussed. Normally, the percussion note is tympanitic. Dullness indicates fluid.
- Puddle sign can detect even a volume as low as 120 mL. Patient lies prone for 5 minutes. The patient is then put in knee–elbow position. Apply the stethoscope on the most dependent part of the abdomen. Repeatedly flick one flank lightly. Diaphragm is moved gradually to the opposite flank. A marked change in the intensity and character of percussion note indicates fluid.

Secondary Effects

- Scrotal oedema.
- Pleural effusion, especially right sided. Pleural effusion develops due to defects in the diaphragm allowing the ascitic fluid to pass into the pleural space.
- Pedal oedema results from hypoproteinaemia and a functional block of IVC due to tense ascites.
- Cardiac apex is shifted upwards due to raised diaphragm.
- Neck veins may be distended secondary to an increase in right atrial pressure, which follows tense ascites and raised diaphragm.
- Meralgia paraesthetica can occur due to compression of lateral cutaneous nerve of thigh.

Investigations

- Ultrasonography is very sensitive in confirming ascites, detecting small amounts of fluid and in identifying the cause.
- Diagnostic paracentesis.
- Laparoscopy and peritoneal biopsy.

Examination of Ascitic Fluid

Investigation	Interpretation
• Gross appearance	
• Clear, straw-coloured or light green	Cirrhosis, congestive heart failure, nephrotic syndrome
• Haemorrhagic	Malignancy, tuberculosis, pancreatitis
• Cloudy, turbid	Bacterial peritonitis
• Deep green	Biliary leak
• Milky white (chylous)	Lymphatic obstruction
• Specific gravity	Less than 1.016 in transudates
	More than 1.016 in exudates
• Protein	Less than 2.5 g/dL in transudates
	More than 2.5 g/dL in exudates
• SAAG	*See below*
• Glucose	Low in malignancy, tuberculosis, peritonitis
• Amylase activity	More than 1000 units/L in pancreatitis
• Microscopy	Less than 250/mm³ in cirrhosis
• Polymorphs	More than 250/mm³ in bacterial peritonitis
• Lymphocytes	Tuberculosis, malignancy
• Gram's stain	Bacterial peritonitis
• Ziehl–Neelsen staining	Tuberculosis
• Cytological examination	Malignancy
• Culture	
• Pyogenic bacteria	Bacterial peritonitis
• Mycobacteria	Tuberculosis

- The ascitic fluid findings specific for individual aetiologies are discussed under the "differential diagnosis of ascites".
- For differences between transudates and exudates, refer the information box.

Differences Between Transudates and Exudates

Feature	Transudate	Exudate
• Appearance	Clear, thin coloured	Turbid, haemorrhagic, straw
• Specific gravity	Less than 1.016	More than 1.016
• Protein	Less than 2.5 g/dL	More than 2.5 g/dL
• Total cell count	Considerably low (<250/µL)	Considerably high (>250/µL)
• Differential count	Mesothelial cells or lymphocytes	Polmorphs, lymphocytes or RBC

Serum-Ascites Albumin Gradient (SAAG)

- A useful prognosticator of portal pressure.
- Calculated by subtracting the ascitic albumin concentration from the serum albumin concentration.
- SAAG ≥1.1 g/dL indicates a high likelihood of portal hypertension.
- SAAG <1.1 g/dL indicates a high possibility of other causes.

- Ascitic fluid total protein level is typically used to define ascitic fluid as transudative (protein content <2.5 g/dL) or exudative (protein content ≥2.5 g/dL). However, many patients with spontaneous bacterial peritonitis have a low rather than high ascitic fluid total protein level and many patients with portal hypertension secondary to heart failure have a high rather than the expected low ascitic fluid total protein level. SAAG is highly sensitive in these cases.

Differential Diagnosis

1. Cirrhosis of Liver

- Clinical features and investigations are discussed under "cirrhosis".
- In cirrhosis the ascitic fluid characteristics are:
  - Clear, straw-coloured or light green.
  - Protein content less than 2.5 g/dL.
  - Polymorphonuclear leucocytes less than 250/mm^3.

2. Constrictive Pericarditis

- Common causes of constrictive pericarditis are:
  - Tuberculosis
  - Rheumatoid arthritis
  - Haemopericardium
  - Idiopathic.
- Because of constriction of the heart, the inflow to heart is reduced resulting in:
  - Decrease in cardiac output.
  - Increase in systemic venous pressure.
- Clinical features
  - Raised JVP with a rapid y descent
  - Pulse is rapid and of low volume
  - Pulsus paradoxus
  - Kussmaul's sign (inspiratory augmentation of JVP)
  - Hepatomegaly
  - Ascites and pedal oedema (late and minimal)
  - Pericardial knock
- Chest radiograph might show a small-sized heart with calcification of pericardium.
- Ascitic fluid is a transudate (unless patient has associated tubercular involvement of peritoneum).
- Echocardiography confirms the diagnosis.
- Treatment includes medical management of the cause and pericardiectomy.

3. Tuberculous Peritonitis

- Tuberculous peritonitis results from one or more of the following:
  - Haematogenous seeding of peritoneum.
  - Lymphatics or mesenteric nodes.
  - Genitourinary source.
- Clinical features
  - Evening rise of temperature, night sweats, weight loss and loss of appetite.
  - Malaise and gradual abdominal distension.
  - "Doughy feel" of the abdomen.
  - Multiple palpable masses in the abdomen caused by matted omentum and loops of intestine.
- Ascitic fluid is usually straw-coloured with a protein concentration more than 2.5 g/dL and lymphocytes more than 70%.
- Acid fast bacilli may be demonstrated by Ziehl-Neelsen staining of ascitic fluid.
- *Tubercle bacilli* may be cultured from ascitic fluid.
- ADA levels are elevated.
- Diagnosis can be confirmed by the peritoneal biopsy of a granuloma under laparoscopy.
- Treatment is antituberculous chemotherapy.

4. Malignant Ascites

- Primaries of stomach, colon, ovary or other intra-abdominal tumours may exude fluid into the peritoneal cavity.
- Any primary malignancy elsewhere may cause ascites by secondary deposits on peritoneal surface.
- Periumbilical subcutaneous tumour deposits are known as "Sister-Joseph's nodules".
- Ascitic fluid characteristics are:
  - Exudate
  - Haemorrhagic
  - High in protein
  - High in specific gravity
  - Sediment contains malignant cells.
- Diagnosis can be confirmed by a laparoscopic biopsy of the peritoneum.
- Treatment is mainly palliative.
  - Repeated paracentesis
  - Intraperitoneal instillation of methotrexate, nitrogen mustard or chloroquine may slow down the rate of reaccumulation of ascites.

5. Pancreatic Ascites

- Pancreatic ascites results from one of the following mechanisms:
  - Disruption of the main pancreatic duct, associated with internal fistula between the duct and peritoneal cavity.
  - Leaking from pancreatic pseudocyst in patients with chronic pancreatitis.
- Previous history suggestive of acute pancreatitis like severe abdominal pain radiating to the back and signs of acute abdomen followed by the development of ascites.
- Ascitic fluid characteristics are:
  - Exudate
  - Haemorrhagic or turbid. Protein more than 2.5 g/dL
  - High levels of amylase (more than 1000 IU/L)
- Serum amylase is elevated.
- ERCP shows passage of contrast material from a major pancreatic duct or pseudocyst into the peritoneal cavity.
- Treatment
  - Nasogastric suction and parenteral alimentation to reduce pancreatic secretions.
  - Ascitic tap to keep the peritoneal cavity free of fluid so as to hasten the sealing of leak. Octreotide (long-acting analogue of somatostatin) inhibits pancreatic secretion and is useful.
  - If there is no response over 2–3 weeks of medical treatment, surgical approach is required which includes stenting of disrupted main pancreatic duct or pancreatic resection.

6. Bacterial Peritonitis

- Acute bacterial peritonitis
- Chronic bacterial peritonitis

Acute Bacterial Peritonitis

- Common causes are appendicitis, perforated viscus like peptic ulcer or typhoid ulcer, cholecystitis, ulcerative colitis, diverticulitis and gangrene of the small bowel.
- Symptoms and signs of acute bacterial peritonitis are:
  - Fever and severe abdominal pain
  - Nausea and vomiting
  - No flatus
  - Thirst
  - "Hippocratic facies"
  - Tachycardia, hypotension and shock
  - Board-like rigidity
  - Tenderness and rebound tenderness
  - Absent peristaltic sounds

- Plain radiograph of abdomen reveals dilated loops of intestine.
- Gas under the diaphragm in cases of perforation.
- Ascitic fluid characteristics are:
  - Exudate
  - Turbid or purulent
  - Presence of intestinal contents in the fluid
  - Cell counts markedly raised
  - Polymorphs more than 250/mm^3
  - Gram staining for bacteria is positive
  - Culture grows the organism.
- Treatment
  - Surgical emergency
  - Correction of fluid and electrolyte disturbances
  - Broad-spectrum antibiotic therapy
  - Measures to combat shock
  - Surgical measures.

Chronic Peritonitis

- Progressive ascites with intermittent subacute intestinal obstruction.
- Ascitic fluid is an exudate, high in protein and contains large number of chronic inflammatory cells.
- Treatment of the underlying cause relieves the condition.

7. Meigs' Syndrome

- Meigs' syndrome is a combination of:
  - Pleural effusion
  - Ascites
  - Non-metastatic pelvic tumour (commonly fibroma of the ovary) in females.
- Pleural effusion is most commonly right sided, may be an exudate or transudate. It is thought to result from movement of ascitic fluid across the diaphragm.
- Both ascites and pleural effusion resolve dramatically following removal of the pelvic tumour.

8. Chylous Ascites

- Due to chyle (intestinal lymph) in the peritoneal cavity.
- Fluid is milky or creamy due to the presence of chylomicrons.
- Common causes of chylous ascites are:
  - Injuries (trauma) to the main lymph ducts in the abdomen
  - Intestinal obstruction if associated with rupture of a major lymphatic channel
  - Congenital lymphangiectasia
  - Malignancy or tuberculosis obstructing the intestinal lymphatics, e.g. lymphoma
  - Filariasis.
- Clinical manifestations are acute abdominal pain with signs of peritoneal irritation and leucocytosis. All these subside leaving the patient with a distended, non-tender, fluid-filled abdomen (chylous ascites).
- Ascitic fluid characteristics are:
  - Milky or creamy
  - High content of fat (triglycerides >1000 mg/dL)
  - Sudan III staining demonstrates fat globules.

9. Budd–Chiari Syndrome

- Refer later.

Q. What are various disorders associated with iron overload?

Q. Discuss the aetiology, pathology, clinical features, investigations and management of hereditary (primary) haemochromatosis ("bronzed diabetes").

Disorders Causing Iron Overload

Hereditary haemochromatosis	Secondary haemosiderosis
	Chronic anaemias
	• β-thalassaemia
	• Sideroblastic anaemia
	• Chronic haemolytic anaemias
	Exogenous. iron overload
	• Multiple blood transfusions
	• Repeated iron injections
	• Prolonged oral iron
	• Chronic liver diseases

- In secondary iron overload iron accumulates in Kupffer cells rather than hepatocytes, as typically occurs in hereditary haemochromatosis.

Hereditary Haemochromatosis

- In haemochromatosis, total body iron is increased to 20–60 g (normal is 4 g).
- High incidence of hepatocellular carcinoma.
- Aetiology
  - Increased absorption of dietary iron over years. Patients with haemochromatosis absorb only a few milligrams of iron in excess of physiological need and thus clinical manifestations often occur at 40–60 years of age, when 20-40 g of excess iron have accumulated.
  - Disease inherited as an autosomal recessive, associated with HLA-B3, B7 and B14 histocompatibility antigens.
  - The gene responsible for the disease is called *HFE* and is located on chromosome 6. This gene is responsible for regulating hepcidin, the primary iron regulatory hormone.
  - 90% of the patients are males. Females are protected by the iron loss in menstruation and pregnancy.
- Pathology
  - Excess iron is deposited in various tissues resulting in damage to liver, pancreas, heart, pituitary gland and skin.
- Clinical features
  - Presents in males over 40 years of age.
  - Cirrhosis with hepatosplenomegaly, loss of libido, testicular atrophy, spiders, loss of body hair, jaundice and ascites.
  - Diabetes mellitus in 30–60% of cases.
  - Heart failure and cardiac arrhythmias.
  - Leaden-grey skin pigmentation due to excess melanin in exposed parts, axillae, groins and genitalia ("bronzed diabetes").
  - Arthritis and chondrocalcinosis.
  - Hypogonadism related to involvement of both pituitary gland and genitalia.
  - Hepatocellular carcinoma in 30% of patients with cirrhosis.
  - A large proportion of patients is asymptomatic and identified by serum iron studies as part of screening studies and screening of family members of an affected individual.
- Investigations
  - Plasma iron concentration is increased.
  - Plasma iron binding capacity—more than 70% is saturated.
  - Transferrin saturation is elevated (>45–50%) which is highly sensitive for diagnosis.
  - Serum ferritin levels are increased to more than 300 μg/L (also increased in alcoholic liver disease, hepatitis C infection, non-alcoholic steatohepatitis and also as acute phase reactant in other inflammatory and neoplastic conditions). Ferritin levels are less sensitive than transferrin saturation in screening tests for haemochromatosis.

- CT scan shows increased density of liver due to iron deposits.
- MRI is sensitive to detect increased hepatic iron content.
- Liver biopsy shows iron deposition and hepatic fibrosis leading on to cirrhosis.
- Management
  - Weekly venesection of 500 mL blood (which removes 250 mg of iron) until the serum iron is normal (may take 2 years or more). Thereafter venesection is continued as required to keep the serum ferritin normal. Blood removed can be used for routine transfusion.
  - In rare cases, who cannot tolerate venesection (because of severe cardiac disease or anaemia), chelation therapy with desferrioxamine has been successful used in removing iron. Dose is 40–80 mg/kg/day subcutaneously. It removes 10–20 mg of iron/day.
  - Treatment of cirrhosis.
  - Treatment of diabetes.
  - Treatment of congestive heart failure and cardiac arrhythmias.
  - Supplemental vitamin C must be avoided as pharmacological doses can accelerate iron mobilisation to a level that saturates circulating transferrin, resulting in an increase in pro-oxidant and free-radical activity.
  - Raw shellfish should be avoided because of *Vibrio vulnificus*, a bacteria that can cause potentially fatal infection and that has been reported in patients with high iron levels.
  - First degree family members should be screened.

Q. Discuss the aetiology, pathology, clinical features, investigations and management of Wilson's disease (hepatolenticular degeneration).

Q. Explain in brief about Kayser–Fleischer ring.

Aetiology

- Autosomal recessive inheritance.
- In Wilson's disease, total body copper is increased due to abnormal copper metabolism.
- There is a failure of biliary copper excretion, causing its accumulation in the body.
- Wilson's disease is characterised by the following abnormalities:
  - Excessive accumulation of copper in the body.
  - Failure to synthesise ceruloplasmin.

Pathology

- The excess copper is deposited in various tissues resulting in damage:
  - Liver
  - Brain (basal ganglia)
  - Eyes
  - Kidneys
  - Skeleton.

Clinical Features

- Presents between 5 and 30 years.
- Dominant features may be hepatic or neuropsychiatric.
  - In childhood and early adolescence hepatic disease dominates.
  - In late adolescence neuropsychiatric manifestations dominate.
- Liver involvement
  - Asymptomatic hepatosplenomegaly
  - Acute hepatitis
  - Fulminant hepatic failure
  - Chronic hepatitis
  - Cirrhosis with portal hypertension
- Brain involvement
  - Characteristically produces neuropsychiatric manifestations.

- Neurological manifestations
  - Movement disorders, especially resting and intention tremors.
  - Less common manifestations include spasticity, rigidity, chorea, dysphagia and dysarthria.
  - Psychiatric manifestations
  - Bizarre behavioural disturbances similar to schizophrenia, manic depressive psychosis and neurosis.
- Eye involvement.
  - Characteristic feature is Kayser–Fleischer rings, due to deposition of copper in the Decemet's membrane of cornea.
    - Greenish-brown or golden-brown ring around the periphery of the cornea, appearing first at the upper periphery. It is best detected by slit-lamp examination.
    - Disappears with treatment.
    - Kayser–Fleischer rings may be associated with "sunflower cataracts".
- Other manifestations
  - Kidney involvement resulting in renal tubular damage
  - Skeletal involvement leading to osteoporosis
  - Arthropathy
  - Cardiomyopathy
  - Haemolysis.

Investigations

- Slit-lamp examination of the eyes for Kayser–Fleischer ring.
- Low serum ceruloplasmin levels (less than 20 mg/dL). Levels can however, be normal in people with ongoing inflammation as it is an acute phase protein.
- Low total serum copper concentration.
- High urinary copper excretion (more than 100 μg/day).
- High hepatic copper content (more than 250 μg/g of dry tissue).

Management

- Chelating drugs
  - Penicillamine 1 g/day (1–4 g/day) lifelong
  - Alternative drug is trientine dihydrochloride 1.2–2.4 g/day.
- Zinc acetate (equivalent to 150 mg zinc every day) for asymptomatic patients or after maximal improvement with penicillamine or trientine. It blocks absorption of copper from intestine. In addition, zinc increases levels of metallothionein in intestinal mucosal cells, which acts as an intracellular ligand that binds copper and holds it until it is excreted in the faeces with desquamated epithelial cells. However, zinc must not be administered with penicillamine or trientine since both the drugs chelate zinc.
- Patients with severe neurologic involvement, who do not improve with penicillamine or trientine, may be treated with intramuscular dimercaprol. Another agent is tetrathiomolybdate that acts by forming a tripartite complex with copper and protein, either in intestinal lumen where it prevents copper absorption or in circulation where it makes copper unavailable for cellular uptake.
- Liver transplantation in fulminant hepatic failure and advanced cirrhosis.
- All siblings of the patient should be screened for Wilson's disease and treated even if they are asymptomatic.

Q. Write a short note on a α_1-antitrypsin.

- An α-1-globulin produced by the liver. It comprises 90% of the α-1-globulin peak seen on serum electrophoresis. It is an acute phase reactant also and is released in response to acute inflammation.
- It is a protease inhibitor (Pi) that inhibits neutrophilic protease enzymes, particularly trypsin. This prevents breakdown of elastin and collagen by proteases.
- There are three forms of α-1-antitrypsins:
  - PiM (medium)
  - PiS (slow)
  - PiZ (very slow)
- PiMM is the normal phenotype while the phenotype PiZZ gives low α-1-antitrypsin concentrations.
- α-1-antitrypsin deficiency is associated with liver disease (cirrhosis) and pulmonary disease (emphysema).
  - In neonates α-1-AT deficiency produces cholestatic jaundice.

- In adults, the manifestations are:
  - Chronic hepatitis
  - Cirrhosis
  - Hepatocellular carcinoma and cholangiocarcinoma
  - Emphysema
  - Chronic bronchitis
  - Others: Panniculitis, vasculitis, pancreatitis and glomerulonephritis.
- Diagnosis
  - Serum protein electrophoresis shows absence of α-1-globulin peak.
  - Low plasma α-1-AT concentration (normal above 150 mg/dL).
  - α-1-AT containing globules can be demonstrated in the liver.
- Treatment
  - Abandon cigarette smoking and alcohol intake.
  - In adult patients (>18 years) with airway obstruction (FEV1 between 35% and 65% of predicted), who have severe deficiency and have stopped smoking, intravenous administration of exogenous α-1-AT derived from pooled human plasma has been shown to be of benefit. Not indicated for correcting liver disease.
  - Liver or lung transplantation.

Q. What is biliary cirrhosis? Discuss the aetiology, pathology, clinical features, investigations and management of primary biliary cirrhosis.

- Biliary cirrhosis is the cirrhosis of the liver secondary to prolonged obstruction of biliary system, anywhere between the small interlobular bile ducts and the papilla of Vater. Obstruction results in progressive destruction of bile ducts.

Primary Biliary Cirrhosis

- Occurs due to chronic inflammation and fibrous obliteration of intrahepatic bile ducts.

Aetiology

- Occurs predominantly in females in the middle age (fifth or sixth decade).
- Due to immune reactions resulting in liver damage.

Pathology

- Chronic granulomatous inflammation destroying the interlobular bile ducts, results in fibrosis and later cirrhosis of the liver and its complications.

Clinical Features

- Asymptomatic patients are discovered on routine examination or investigations.
- Cardinal features are pruritus, hyperpigmentation and jaundice.
- Usually pruritus occurs months to years before jaundice. It is more at night.
- Liver involvement
  - Intense pruritus, probably due to bile salts.
  - Progressive jaundice, later becoming intense.
  - Patient acquires a "bottle green colour."
  - Scratch marks and finger clubbing.
  - Hepatosplenomegaly.
  - Hepatocellular failure, portal hypertension and ascites.
- Hypercholesterolaemia
  - Xanthelasmas around the eyes.
  - Xanthomas over joints, tendons, hand creases, elbows and knees.
  - Pain, tingling and numbness over feet and hands due to peripheral neuropathy resulting from lipid infiltration of peripheral nerves.
- Malabsorption
  - Steatorrhoea and diarrhoea from malabsorption of fat.
  - Easy bruising and ecchymosis from vitamin K deficiency.

- "Hepatic osteodystrophy"—bone pains and fractures due to osteomalacia and osteoporosis resulting from malabsorption of vitamin D.
- Night blindness due to vitamin A deficiency.
- Dermatitis due to vitamin E deficiency.
- Associated diseases
  - Sicca syndrome
  - Thyroid diseases
  - CRST syndrome (calcinosis, Raynaud's phenomenon, sclerodactyly and telangiectasia)
  - Scleroderma.

Investigations

- Hyperbilirubinaemia of the conjugated type.
- Mild elevation of transaminases.
- Two to five fold rise of serum alkaline phosphatase.
- Marked rise of serum 5′-nucleotidase activity.
- Hyperlipidaemia.
- More than 90% of the patients have antimitochondrial antibodies (IgG type) and increased levels of cryoproteins consisting of immune complexes.
- Antinuclear, antismooth muscle antibodies.
- Elevated immunoglobulins especially IgM.
- Ultrasound of abdomen may show lymph nodes.
- MRCP shows normal biliary tree.
- Liver biopsy confirms the diagnosis.

Management

- Ursodeoxycholic acid (10–15 mg/kg) improves bilirubin and aminotransferase values. It appears to exert its beneficial effects by rendering bile composition less toxic for the injured biliary epithelium, reducing the retention of bile acids in hepatocytes and inhibiting bile-induced apoptosis of hepatocytes.
- Steroids may improve biochemical and histological disease but may lead to osteoporosis.
- Other therapies like azathioprine, colchicine, methotrexate and cyclosporin have shown some benefit in minority of patients.
- Steatorrhoea is treated by limiting fat intake and substituting long-chain triglycerides with medium-chain triglycerides in the diet.
- Monthly injections of vitamin K.
- Vitamin D (calciferol 1 mg/day) or alphacalcidol 1 µg/day.
- Calcium supplementation.
- Bisphosphonates (e.g. alendronate) to reduce osteoporosis.
- Liver transplantation.
- Management of pruritus
  - Cholestyramine 4–16 g/day
  - Antihistamines
  - Rifampicin, ondansetron and opiate antagonists (naloxone and naltrexone) have shown some benefit.

Q. What is meant by secondary biliary cirrhosis?

- Secondary biliary cirrhosis results from prolonged obstruction to large biliary ducts by:
  - Stones
  - Bile duct strictures
  - Sclerosing cholangitis.
- Patients with malignant tumours of bile duct or pancreas rarely survive long enough to develop secondary biliary cirrhosis.
- Clinical features
  - Recurrent abdominal pain in stones.
  - Fluctuating jaundice in stones.
  - Previous history of abdominal surgery in strictures.

- Chronic cholestasis with episodes of ascending cholangitis and even liver abscess.
  - Right upper quadrant pain due to cholangitis or biliary colic.
  - Cirrhosis, ascites and portal hypertension are late features.
- Investigations
  - Hyperbilirubinaemia of the conjugated type.
  - Markedly elevated serum alkaline phosphatase activity.
  - Ultrasound and CT of abdomen.
  - ERCP or MRCP.
  - Liver biopsy.
- Treatment
  - Relief of obstruction to bile flow by ERCP or surgery.
  - Antibiotics in sclerosing cholangitis.

Q. What is cardiac cirrhosis?

- Prolonged severe right-sided congestive heart failure leads to cardiac cirrhosis.
- In right heart failure there is retrograde transmission of elevated venous pressure via the IVC and hepatic vein, into the liver. This leads to hepatic congestion. With prolonged passive venous congestion liver becomes enlarged, tender and ultimately results in cirrhosis. Examination of liver shows a "nutmeg liver" (alternating red-congested and pale-fibrotic areas).
- Clinical features
  - Symptoms and signs of severe right heart failure.
  - More important is a chronic encephalopathy with a waxing and waning course.
- Diagnosis
  - Firm enlarged liver with signs of chronic liver disease in a patient with valvular heart disease, constrictive pericarditis or cor pulmonale of long duration (more than 10 years).
  - Liver non-pulsatile despite presence of tricuspid regurgitation.
  - Liver biopsy confirms the diagnosis (not required in most cases).
- Treatment is that of the underlying cardiovascular disorder.

Q. Write a short note on non-cirrhotic portal fibrosis (NCPF).

- Idiopathic non-cirrhotic portal hypertension (INCPH) is characterised by an increased portal venous pressure gradient in the absence of a known cause of liver disease and portal vein thrombosis. Common causes are schistosomiasis, non-cirrhotic portal fibrosis, non-alcoholic steatohepatitis, primary biliary cirrhosis and primary sclerosing cholangitis.
- NCPF is an idiopathic disease characterised by periportal fibrosis and involvement of small and medium branches of portal vein, resulting in development of portal hypertension and splenomegaly but without features of liver cell failure.
- Postulated aetiologies include bacterial infections, exposure to toxins (particularly arsenic), immunological abnormalities and hypercoagulable states.
- The diagnosis is considered in patients with no evidence of cirrhosis or extrahepatic portal vein obstruction.
- The disease is characterised by upper GI bleed, massive splenomegaly with anaemia, preserved liver function and benign prognosis in a majority of patients.
- Development of ascites, jaundice and hepatic encephalopathy are uncommon and may be seen only after an episode of gastrointestinal haemorrhage.
- In late stages, nodular transformation can occur when the patient may develop some features of cirrhosis and ascites.
- Liver function tests are usually normal. Pancytopenia may occur due to hypersplenism.
- On Doppler ultrasound, splenoportal axis and hepatic veins patent
- Splenoportovenography (SPV) showed massive dilatation of the portal and splenic veins and the presence of collaterals.
- Liver histology demonstrates maintained lobular architecture, portal fibrosis of variable degree, sclerosis and obliteration of small-sized portal vein radicals and subcapsular scarring with collapse of the underlying parenchyma.
- Treatment is endoscopic sclerotherapy or banding to prevent variceal bleed and shunt surgery.

Q. Discuss the aetiology, pathology, clinical features, investigations and management of hepatic venous outflow tract (HVOT) obstruction.

Q. Explain briefly about Budd–Chiari syndrome.

Q. Describe veno-occlusive disease or sinusoidal obstruction syndrome.

- Obstruction to the hepatic venous outflow [hepatic venous outflow tract (HVOT) obstruction] can occur at the following levels:
  - Central hepatic veins → Veno-occlusive disease
  - Large hepatic veins → Budd–Chiari syndrome
  - IVC

Budd–Chiari Syndrome

Definition

- Budd–Chiari syndrome is characterised by obstruction of hepatic venous outflow at any level from the small hepatic veins to the junction of the IVC with the right atrium. This term does not include cardiac or pericardial causes of hepatic outflow obstruction.
- Budd–Chiari syndrome comprises a triad of abdominal pain, ascites and hepatomegaly with hepatic histology showing centrizonal sinusoidal distension and pooling.

Aetiology

Hepatic vein obstruction	IVC obstruction
• Venous thrombosis	• Congenital
• Polycythaemia vera	• Webs
• Antiphospholipid syndrome	• Diaphragms
• Pregnancy and post-partum period	• Thrombosis
• Use of oral contraceptives	• Renal cell carcinoma
• Sickle cell disease	• Hepatoma
• Paroxysmal nocturnal haemoglobinuria	• Myeloproliferative syndrome
• Other hypercoagulable diseases	• Vasculitis
• Compression (may also produce thrombosis)	• Behcet's syndrome
• Liver abscess	• Idiopathic
• Hydatid cyst	
• Radiation injury	
• Webs (congenital)	

Pathology

- In the initial stages, liver shows centrilobular venous dilatation and congestion, with haemorrhage and central necrosis of hepatocytes.
- In the later stages, centrilobular fibrosis develops and the picture is that of cardiac cirrhosis.

Clinical Features

- Fulminant form (fulminant Budd–Chiari syndrome).
  - Presents with fulminant hepatic failure due to liver necrosis. Ascites and renal failure are present.
- Acute form (acute Budd–Chiari).
  - Develops over a month or so and follows sudden venous occlusion (renal cell carcinoma, hepatoma and polycythaemia).
  - Presents with acute abdominal pain, vomiting, tender hepatomegaly, ascites and mild jaundice.
  - If venous occlusion is total, delirium, coma and hepatocellular failure develop.
- Subacute form (subacute Budd–Chiari)
  - Insidious onset
  - Ascites and hepatic necrosis may be minimal, because the hepatic sinusoids have been decompressed by a portal and hepatic venous collateral circulation.

- Chronic form (chronic Budd–Chiari).
  - More usual presentation.
  - Pain in abdomen, tender hepatomegaly and ascites.
  - Icterus is mild or absent.
  - Negative hepatojugular reflux—i.e. pressure over the liver or other parts of abdomen fails to fill the jugular veins.
  - Gradual development of portal hypertension and splenomegaly.
  - Enlarged caudate lobe of the liver becomes palpable.
  - IVC obstruction manifests itself as bilateral pedal oedema and distended veins over abdomen, flanks and back.
  - Hepatocellular carcinoma may develop.
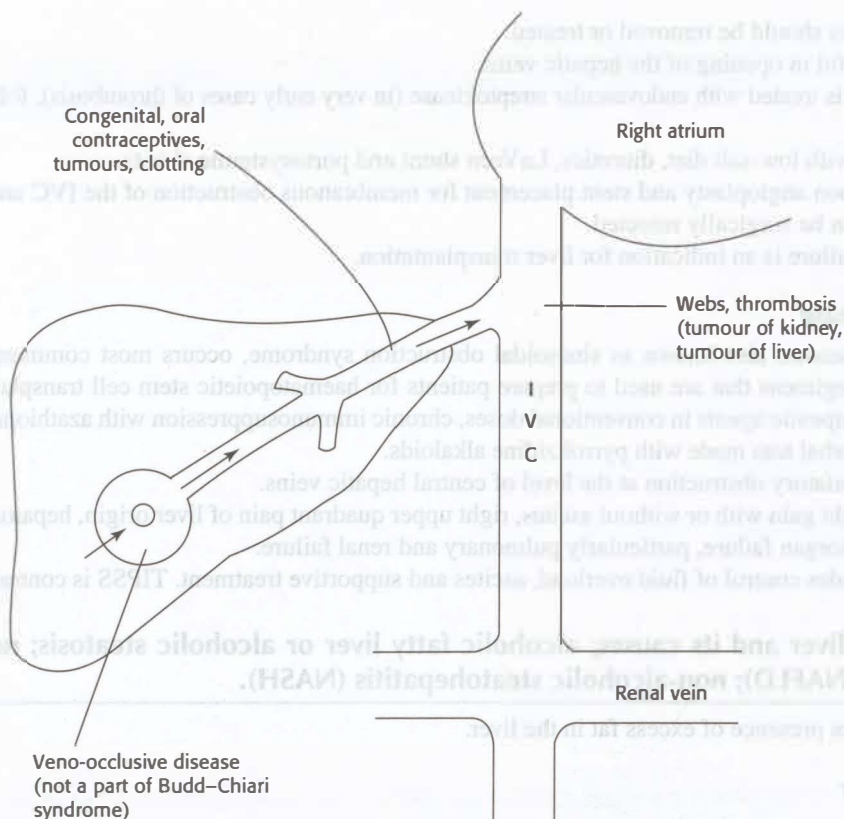
Aetiological factors in Budd–Chiari syndrome

Investigations

- Liver function tests reveal mild hyperbilirubinaemia, raised alkaline phosphatase, low serum albumin and raised transaminases.
- Ascitic fluid examination typically shows a protein concentration more than 2.5 g/dL in the early stages.
- Ultrasound may show enlargement of the caudate lobe, intrahepatic collaterals, echogenic areas consistent with occlusion of hepatic veins and ascites.
- Doppler ultrasonography can detect abnormality of venous flow with high accuracy, and this may be sufficient to establish the diagnosis.
- Liver biopsy shows centrilobular congestion with fibrosis.
- Non-invasive CT or MRI hepatic venography.
- Hepatic venography to determine extent of block and caval pressures.

Management

- Predisposing causes should be removed or treated.
- TIPSS may be useful in opening of the hepatic veins.
- Recent thrombosis is treated with endovascular streptokinase (in very early cases of thrombosis), followed by heparin and warfarin.
- Ascites is treated with low-salt diet, diuretics, LeVeen shunt and portosystemic shunts.
- Percutaneous balloon angioplasty and stent placement for membranous obstruction of the IVC and hepatic vein.
- Congenital web can be surgically resected.
- Progressive liver failure is an indication for liver transplantation.

Veno-Occlusive Disease

- Veno-occlusive diseases, also known as sinusoidal obstruction syndrome, occurs most commonly as a complication of myeloablative regimens that are used to prepare patients for haematopoietic stem cell transplantation. Other causes include chemotherapeutic agents in conventional doses, chronic immunosuppression with azathioprine or 6-thioguanine, and ingestion of herbal teas made with pyrrolizidine alkaloids.
- Occurs due to circulatory obstruction at the level of central hepatic veins.
- Presents with weight gain with or without ascites, right upper quadrant pain of liver origin, hepatomegaly and jaundice.
- May develop multiorgan failure, particularly pulmonary and renal failure.
- Management includes control of fluid overload, ascites and supportive treatment. TIPSS is contraindicated.

Q. Discuss fatty liver and its causes; alcoholic fatty liver or alcoholic steatosis; non-alcoholic fatty liver disease (NAFLD); non-alcoholic steatohepatitis (NASH).

- Fatty liver indicates presence of excess fat in the liver.

Causes of Fatty Liver

Alcohol

Non-alcoholic fatty liver disease (NAFLD) [Non-alcoholic steatosis and non-alcoholic steatohepatitis (NASH)]

1. Drugs
- Glucocorticoids
- Amiodarone
- Aspirin
- Tetracyclines
- Methotrexate
- Zidovudine
- Didanosine
- Tamoxifene
- Amiodarone

2. Nutritional
- Protein-calorie malnutrition
- Total parenteral nutrition
- Rapid weight loss/obesity

3. Metabolic
- Lipodystrophy
- Pregnancy (acute fatty liver)
- Diabetes

4. Miscellaneous
- Inflammatory bowel disease
- HIV infection
- Reye's syndrome
- Toxic mushrooms (*Amanita phalloides*)
- Obstructive sleep apnoea
- Indian childhood cirrhosis
- Chronic hepatitis C

Alcoholic Steatosis and Steatohepatitis

- The severity of fatty involvement is roughly proportional to the duration and degree of alcohol intake.
- Most common feature is hepatomegaly with or without tenderness or discomfort.
- Occasionally, patients develop icterus and nausea.
- Many patients may develop cirrhosis of liver with its associated complications.
- Laboratory features include elevated ALT and aspartate aminotransferase (AST) with AST:ALT >1.
- Ultrasound shows diffuse increase in echogenicity as compared to the kidneys and spleen.
- On CT scan, fatty infiltration produces a low-density liver as compared to spleen.
- Treatment is complete abstinence of alcohol and nutritional support.

Non-Alcoholic Fatty Liver Disease (NAFLD), Non-Alcoholic Steatosis and Non-Alcoholic Steatohepatitis (NASH)

- Non-alcoholic fatty liver disease (NAFLD) is classified into two categories: simple fatty liver (non-alcoholic steatosis) with a favourable clinical outcome and non-alcoholic steatohepatitis (NASH), which is intractable and progressive.
- Important risk factors for development of this entity are obesity, type 2 diabetes mellitus, hyperlipidaemia and insulin resistance.
- Adipocytokines secreted from adipocytes in individuals with visceral fat obesity are closely associated with the occurrence of NASH. NASH is considered to be induced by two consecutive steps: excess fat accumulation and subsequent necroinflammation in the liver.
- Non-alcoholic fatty liver is a common cause for abnormal liver tests.
- Most patients have no symptoms at the time of diagnosis, although some have fatigue, malaise and a sensation of fullness in the upper abdomen. Other features may include daytime sleepiness and autonomic disturbances. Hepatomegaly is the only sign in most patients. Many patients are obese.
- Patients with simple steatosis generally have a benign course whereas many with NASH show progression to cirrhosis and sometimes to hepatocellular carcinoma. Many patients with cryptogenic cirrhosis are likely to represent cases of previously unrecognised NASH, particularly because hepatic steatosis may disappear with the development of cirrhosis.
- Incidence of coronary artery disease increased in patients with NASH.
- Laboratory features include intermittent elevation in ALT and AST with AST:ALT <1. This ratio increases as fibrosis advances.
- Ferritin levels increased in 20–50% of patients.
- Autoantibodies (e.g. antinuclear and anti-smooth muscle antibodies) identified in nearly 25% of patients and may be associated with more advanced fibrosis.
- Ultrasound and CT features are similar to those in alcoholic fatty liver.
- Liver biopsy remains the best diagnostic tool for confirming fatty liver disease. It is also the most sensitive and specific mean of providing important prognostic information by distinguishing steatosis from NASH and by determining the stage of fibrosis.
- Treatment includes control of weight, diabetes and hyperlipidaemia. No drug is recommended at present though several drugs like metformin, pioglitazone, ursodeoxycholic acid (UDCA), pentoxyphylline and atorvastatin have shown some promise.

Q. Discuss the aetiology, clinical features, investigations and management of hepatocellular carcinoma (hepatoma).

- Hepatoma is the most common primary malignancy of liver.
- Most common in Africa and south-east Asia.

Aetiology

• Chronic HBV infection	• α-1 antitrypsin deficiency
• Chronic hepatitis C virus infection	• Wilson's disease
• Aflatoxin (a fungal toxin contaminating food)	• Thorotrast and arsenic exposure
• Alcoholic cirrhosis	• Oestrogens and androgens
• Primary biliary cirrhosis	• Anabolic steroids
• Haemochromatosis	• Non-alcoholic steatohepatitis (NASH)
• Obesity	• Betel quid chewing

Clinical Features

- Usually occurs in patients with underlying cirrhosis.
- Non-specific symptoms like weakness, anorexia, weight loss and fever.
- Hepatomegaly with pain or tenderness is the most common presentation (more than 50%).
- Friction rub or bruit over the liver.
- Blood-tinged ascites.

- Metabolic disturbances (paraneoplastic features) include polycythaemia, hypoglycaemia, hypercholesterolaemia, acquired porphyria and hypercalcaemia.
- Intravascular invasion and growth into portal vein or IVC is a common feature.

Investigations

- Very high levels of serum alkaline phosphatase.
- A markedly increased (>500 μg/L) or rising levels of α-foetoprotein.
- Ultrasonography
- CT scan of abdomen (triple-phase) or MRI abdomen.
- Liver scintigraphic scans.
- Hepatic artery angiography shows "tumour blushes".
- Liver aspiration or biopsy confirms the diagnosis.

Management

- Curative intent (lesions 1–3 in number and <5 cm in size; no metastasis; compensated underlying liver disease with Child score A) possible in only 15% cases as most present with advanced disease.
    - Surgical removal (after successful resection tumour recurs in the cirrhotic liver in about 70% of patients after 5 years).
    - Percutaneous ethanol injection (PEI) or percutaneous acetic acid injection (PAI).
    - Percutaneous radiofrequency thermal ablation.
- Palliative therapy
    - PEI or acetic acid injection
    - Transcatheter arterial chemoembolisation (TACE)
    - Transcatheter arterial embolisation
    - Percutaneous radiofrequency thermal ablation
    - Transarterial radioembolisation (TARE) with intra-arterial injection of yttrium-90 microspheres (^{90}Y).
    - Chemotherapy using sorafenib (a multikinase inhibitor).
- Liver transplant is an option in presence of localised tumour and underlying advanced liver disease.

Q. Discuss briefly about liver transplantation.

- Transplantation of liver is useful in a patient with end-stage liver disease or fulminant liver failure.
- 5-year survival in good centres is as high as 75%.
- Orthotopic liver transplantation—implantation of a donor organ after removal of the native organ in the same anatomic location. Most common form of liver transplantation.
- Auxiliary Partial Orthotopic Liver Transplantation (APOLT)
    - It is a technique where part of the native liver is removed and replaced with either the respective left or right lobe of a graft.
    - The advantage is that the native liver is retained and if sufficient hepatic regeneration was to occur immunosuppression could be withdrawn and the liver graft allowed to atrophy or be surgically removed.
    - There are, however, several conditions where this procedure would not be appropriate; those in which the native liver is already cirrhotic or where there is a risk of hepatic malignancy (e.g. tyrosinaemia, multicentric hepatocellular carcinoma).
- Living donor liver transplantation—a portion of healthy person's liver is removed and used for transplantation.
- Bioartificial liver
    - Cultured hepatocytes are used as bridge in patients with acute liver failure till donor liver becomes available.
    - Have the capacity to remove toxins and provide synthetic functions of liver.
    - Results are controversial.

Indications

- Fulminant hepatic failure.
- Decompensated cirrhosis (including hepatorenal syndrome) due to any cause.
- Hepatocellular carcinoma with no single lesion greater than 5 cm or no more than three lesions with the largest being 3 cm or smaller.
- Biliary atresia.
- Inherited diseases
    - Wilson's disease
    - Glycogen storage diseases
    - Crigler–Najjar syndrome type I

- Familial hypercholesterolaemia
- α-1-antitrypsin deficiency.

Contraindications

- Absolute contraindications
  - Expected outcome of transplantation is poor (e.g. multisystem organ failure, extrahepatic or extrabiliary malignancy or infection, advanced cardiac or pulmonary disease, human immunodeficiency virus infection and active alcohol or illicit substance abuse).
- Relative contraindications
  - Comorbidities with potential to reduce survival (e.g. renal insufficiency, primary hepatobiliary malignancy >5 cm, haemochromatosis, spontaneous bacterial peritonitis, age older than 65 years, poor social support and the inability to comply with immunosuppressive treatment).

Complications

- Hepatic complications
  - Graft failure due to ischaemia
  - Failure or obstruction of biliary anastomosis
  - Graft rejection
  - Jaundice (related to transfusion of blood, release of haem from collections of blood, use of drugs and anaesthetic agents, ischaemic injury due to shock, sepsis, hepatitis, biliary obstruction).
- Non-hepatic complications
  - Fluid overload
  - Renal dysfunction
  - Intraperitoneal bleeding
  - Infections.

Immunosuppressive Treatment

- Most commonly, corticosteroids along with tacrolimus or cyclosporin are used.

Q. Discuss the aetiology, clinical features, investigations and management of pyogenic liver abscess (bacterial liver abscess).

- Aetiology
  - Bacteria reach the liver and cause abscess by one of the following five mechanisms:
    - Portal vein bacteraemia from appendicitis, diverticulitis and perforated bowel.
    - Systemic bacteraemia reaching liver via hepatic artery.
    - Ascending cholangitis.
    - Direct extension from a contiguous focus of infection like subphrenic abscess.
    - Penetrating trauma introducing the bacteria into liver or blunt trauma resulting in a hepatic haematoma that gets secondarily infected.
  - Single abscesses are more common in the right lobe of the liver. Multiple abscesses are seen in elderly patients, usually due to ascending cholangitis.
  - Common organisms are *E. coli*, *K. pneumoniae*, *S. aureus*, anaerobic streptococci and bacteroides.
- Clinical features
  - Most have a subacute onset
  - Fever with chills and rigors
  - Weight loss, anorexia, nausea and vomiting
  - Right upper quadrant pain radiating to right shoulder
  - Pleuritic chest pain
  - Tender hepatomegaly
  - Mild jaundice
  - Respiratory findings at the base of right lung (pleural effusion, crepitations).
- Investigations
  - Leucocytosis and raised ESR
  - Mildly elevated serum bilirubin
  - Markedly elevated serum alkaline phosphatase
  - Low serum albumin

- Blood culture may be positive
- Chest radiograph shows raised right dome of diaphragm, right basilar atelectasis and pneumonia or effusion
- Ultrasonography confirms the diagnosis
- CT scan of abdomen if clinical suspicion is strong but ultrasound is normal.
- Needle aspiration of pus for culture sensitivity.
- Management
  - Commence treatment with a combination of ampicillin, gentamicin and metronidazole. Later, change the antibiotic according to the sensitivity reports. Duration is 4–8 weeks.
  - Ultrasound-guided aspiration of the abscess. Indications include:
    - Abscess size is large (>6 cm).
    - Left lobe abscess.
    - Lack of response after 48–72 hours of medical therapy.
    - Ultrasonographic picture suggestive of large abscess with impending rupture.
- Surgical drainage for those who fail to respond or have multiloculated abscess, abscess with thick pus, multiple abscesses or left lobe abscess.

Q. Discuss the differential diagnosis of jaundice of 3 weeks' duration in an elderly person.

- Viral hepatitis
- Drug-induced hepatitis
- Gallstone disease
- Hepatoma
- Alcoholic hepatitis

- Weil's disease
- Cirrhosis of liver
- Secondaries in liver
- Carcinoma of head of pancreas

Q. What are the common causes of hepatomegaly with tenderness (tender hepatomegaly)?

- Hepatitis
  - Viral hepatitis
  - Drug-induced hepatitis
  - Alcoholic hepatitis
  - Chronic hepatitis

- Congestive cardiac failure
- Amoebic liver abscess
- Pyogenic liver abscess
- Acute Budd–Chiari syndrome
- Hepatoma—late feature
- Secondaries—occasionally

Q. Enumerate the common causes of splenomegaly?

Causes

Mild enlargement (up to 5 cm)	Moderate enlargement (5–8 cm)	Massive splenomegaly (more than 8 cm)
Malaria	Cirrhosis of liver	Chronic malaria
Typhoid	Lymphomas	Kala-azar
Infective endocarditis	Leukaemias	Chronic myeloid leukaemia
Disseminated tuberculosis	Infectious mononucleosis	Extrahepatic portal vein obstruction
Viral hepatitis	Haemolytic anaemias	Thalassaemia major
Disseminated fungal infection	Splenic abscess	Myelofibrosis
Septicaemia	Amyloidosis	Myeloid metaplasia
Thalassaemia minor	Haemochromatosis	Hairy cell leukaemia
Rheumatoid arthritis	Polycythaemia vera	Gaucher's disease
Systemic lupus erythematosus		Niemann–Pick disease
HIV infection		Sarcoidosis
Congestive cardiac failure		Splenic cysts

Chapter 7

Diseases of the Cardiovascular System

Q. Discuss the differential diagnosis of chest pain.

Common Causes of Chest Pain

Cardiac	Aortic	Oesophageal
• Angina pectoris	• Dissecting aneurysm	• Reflux oesophagitis
• Myocardial infarction	**Lung and pleura (respiratory)**	• Diffuse oesophageal spasm
• Mitral valve prolapse	• Pleurisy	**Musculoskeletal**
• Pericarditis	• Pneumothorax	
• Hypertrophic cardiomyopathy	• Pulmonary embolism	**Hyperadrenergic state**
• Aortic stenosis/regurgitation	**Intra-abdominal conditions**	• Cocaine intoxication
		Anxiety

- Respiratory chest pain most commonly arises from parietal pleura (including the diaphragmatic pleura), chest wall and the mediastinal structures. Lung parenchyma and visceral pleura are insensitive to most painful stimuli. The peripheral part of the diaphragm and costal portion of parietal pleura are innervated by somatic intercostal nerves, thus pain felt in these areas is often localised to cutaneous distribution of involved neurons over the adjacent chest wall. Central portion of diaphragm is innervated by phrenic nerve; therefore central diaphragm irritation is referred to ipsilateral shoulder tip or even the neck.

Angina Pectoris

- Pain is usually retrosternal in location and brought on by exertion. It is relieved by rest and sublingual nitrates. Pain seldom lasts more than 20 minutes. Character of the pain is squeezing, crushing or aching. Pain commonly radiates to left arm and less commonly to right arm, throat, back, chin and epigastrium. Often the pain comes on while walking uphill after a heavy meal on a cold winter day.
- The following physical signs are those of "myocardial ischaemia". The presence of one or more of them during an attack of pain may be suggestive.

• Rise in blood pressure and heart rate	• Dyskinetic segment around the apex
• Fourth heart sound	• Paradoxical splitting of second heart sound
• Murmur of mitral regurgitation due to papillary muscle dysfunction	• Relief of pain by carotid sinus massage (Levine test)

- Salient investigations include electrocardiography, echocardiography, exercise testing and coronary angiography.

Myocardial Infarction

- A history of previous episodes of anginal pain with recent worsening may be present. The pain of infarction is similar in character and distribution is similar to anginal pain. But it is more severe, prolonged (lasts more than 20 minutes), persisting at rest and not responding to nitrates. There may be vomiting, anxiety and a feeling of impending death.
- One or more of the physical signs of myocardial ischaemia may be present (refer above).
- Other common physical signs include pallor, sweating, cyanosis, hypotension, arrhythmias (most commonly ventricular ectopic beats), pericardial friction rub, signs of congestive heart failure and cardiogenic shock.
- Salient investigations include serial electrocardiograms and cardiac injury enzymes.

Mitral Valve Prolapse

- History of non-specific chest pain is atypical.
- Physical findings include a mid-systolic click and a late systolic murmur varying with posture and respiration.
- Echocardiography can confirm the diagnosis.

Pericarditis

- Pericardial pain is felt retrosternally to the left of the sternum or in the left or right shoulder. Pain is aggravated by deep breathing and rotating the trunk. It is worse in the lying down position and is relieved by sitting up and leaning forwards.
- Physical findings include the characteristic pericardial friction rub and evidence of pericardial effusion.
- Salient investigations include electrocardiography and echocardiography.

Dissecting Aneurysm of Aorta

- Sudden onset of severe, sharp, stabbing or tearing pain over the anterior chest radiating to the back is the usual history. Dissection is more common in hypertensive males.
- Physical findings include asymmetry of brachial, carotid or femoral pulses, inappropriate bradycardia and an early dia-stolic murmur or aortic regurgitation. Neurological features (hemiparesis, paraparesis, etc.) may develop due to carotid artery or spinal artery involvement.
- Salient investigations include chest radiography, echocardiography, CT scanning and aortography.

Pleurisy

- Can occur due to inflammation, infection, neoplastic infiltration or trauma.
- Pleuritic pain is a well-localised pain that is cutting, stabbing or tearing in character. It is often aggravated by coughing, sneezing and deep inspiration. Commonest sites of pleuritic pain are axillae and beneath the breasts.
- Characteristic sign is a pleural friction rub.

Pneumothorax

- History of sudden onset dyspnoea and chest pain following strenuous exertion or coughing. More common in tall, thin, young males.
- Clinical features may include cyanosis, tachycardia, hypotension and distended neck veins. Respiratory system exami-nation reveals shift of the mediastinum (trachea and apex beat) to the opposite side, reduced chest movements, hyper-resonant percussion note, diminished vocal fremitus and vocal resonance, and markedly reduced to absent breath sounds.
- Diagnosis is confirmed by chest radiography.

Acute Pulmonary Embolism

- Characteristic clinical setting may be obvious, e.g. prolonged immobilisation, recent surgery, previous history of throm-boembolism or intake of oral contraceptives.
- Clinical examination may reveal calf muscles tenderness, tachypnoea and tachycardia. Respiratory system examina-tion may show a variety of physical signs like crepitations over the involved area, pleural rub or pleural effusion. Cardiovascular system examination may show evidences of acute right ventricular failure including a right-sided third heart sound, murmur of pulmonary regurgitation or increased intensity of the pulmonary component of second heart sound. However, examination may be entirely normal.
- Salient investigations include chest radiography, electrocardiogram, echocardiography, helical CT scan and radionu-clide ventilation/perfusion scan.

Reflux Oesophagitis

- Characteristic history is "heart burn", felt as a burning pain behind the sternum, radiating to the throat. It typically occurs after heavy meals and is brought on by bending, lifting or straining. Pain may occur on lying down in bed at night but relieved by sitting up. Other symptoms of gastro-oesophageal reflux are odynophagia and regurgitation of gastric contents into the mouth.
- Salient investigations include oesophagoscopy, barium studies and acid infusion studies. Often, a sliding hiatus hernia predisposes to reflux.

Diffuse Oesophageal Spasm

- Pain can mimic that of angina and is sometimes precipitated by exercise and relieved by nitrates. Usually the pain is related to food or drink intake. Dysphagia is often present.
- Salient investigations include oesophageal motility studies, barium studies and manometry.

Musculoskeletal Pain

- Common causes of musculoskeletal pains are:
  - Intercostal myalgia
  - Costochondritis (Tietze's syndrome)
  - Fracture of the ribs (cough, trauma)
  - Secondaries in the ribs
  - Intercostal neuralgias
- Pain is usually well localised, variable in intensity and site, varying with posture and movement.
- Usually associated with severe local tenderness.

Intra-Abdominal Conditions

- Intra-abdominal conditions can occasionally present as chest pain. These include the following:
  - Acute pancreatitis
  - Acute cholecystitis
  - Perforated peptic ulcer

Q. Give a brief account of mechanism, causes, consequences and management of Cheyne–Stokes breathing.

Definition

- This is a form of periodic breathing characterised by alternating periods of central apnoea (or hypopnoea) and hyperpnoea.
- The rate and depth of respiration increase to a maximum over a period of a few minutes, then decrease until breathing virtually ceases. The patient lies motionless for 10–20 seconds (apnoea). Then the cycle is repeated.

Mechanism

- Anoxaemia abolishes the spontaneous rhythmic activity of breathing. Consequent apnoea results in accumulation of carbon dioxide. This hypercapnia stimulates respiratory centres resulting in hyperventilation. The hyperventilation leads to carbon dioxide wash out and results in depression of the respiratory centre leading to apnoea. The cycle is repeated.
- Apnoeas are more severe when the patient is supine because pulmonary congestion worsens on lying flat, which activates afferent receptors present in lung ("J" receptors) and induces hyperventilation.

Conditions Associated with Cheyne–Stokes Breathing

• Severe heart failure	• Increased intracranial pressure
• Uraemia	• Severe pneumonia
• Chronic hypoxia	• Narcotic drug poisoning
• Cerebral trauma and haemorrhage	• Normal subjects living at high altitude

Consequences

- Alternating cycles of hyper- and hypoventilations provoke oscillations in blood pressure, heart rate and tidal volume. This leads to a state of physiological instability in the already stressed cardiovascular system in patients with congestive heart failure (CHF).
- Poor sleep quality leads to daytime somnolence, fatigue, impaired quality of life and insomnia.

Management

- Treatment of underlying cause.
- In patients with CHF, theophylline, acetazolamide or benzodiazepines have been used with varying success.
- Oxygen therapy.
- Positive pressure ventilation.

Q. Discuss the approach to a patient with palpitations.

- Described as an uncomfortable awareness of one's own heartbeat.
- Occurrence of palpitations does not necessarily mean that an arrhythmia is present; conversely, an arrhythmia can occur without palpitations.

Causes of Palpitations

Cardiac arrhythmias
- Paroxysmal atrial flutter/fibrillation
- Paroxysmal supraventricular tachycardia
- Premature atrial contractions
- Sick sinus syndrome
- Sinus tachycardia
- Premature ventricular contractions
- Ventricular tachycardia

High cardiac output states
- Anaemia
- Arteriovenous fistula
- Beriberi
- Fever
- Paget's disease
- Pregnancy
- Thyrotoxicosis

Cardiac abnormalities
- Atrial myxoma
- Congenital heart disease (atrial septal defect, patent ductus arteriosus, ventricular septal defect)
- Mitral valve prolapse
- Pacemaker (function or failure)
- Prosthetic heart valves
- Aortic or mitral regurgitation

Drug-induced
- Alcohol (use or withdrawal)
- Amphetamines
- Anticholinergic agents
- Caffeine, nicotine
- Cardiac glycosides
- Cocaine
- Epinephrine
- Nitrates

Metabolic
- Hyperthyroidism
- Hypoglycaemia
- Pheochromocytoma

Psychiatric causes
- Generalised anxiety
- Hypochondriasis
- Major depression
- Panic disorder

Miscellaneous
- Emotional stress
- Hyperventilation
- Premenstrual syndrome
- Scombroid fish poisoning
- Strenuous physical activity

Evaluation

- Primary goals are:
  - To detect and identify presence and nature of any underlying arrhythmia.
  - To determine the presence of organic heart disease.
  - To determine the presence of precipitating causes.

History

Character of Palpitations

- Helpful to ask patients to tap out the rhythm of their palpitations to identify regularity and speed.
- A feeling of "flip-flopping" in chest is usually secondary to a premature atrial or ventricular beat.
- A feeling of stoppage of heart is usually secondary to the pause that follows a premature beat.
- A feeling of pounding is usually due to a forceful beat caused by post-extrasystolic potentiation after a premature beat.
- A feeling of rapid fluttering in chest is usually secondary to supraventricular or ventricular tachyarrhythmias.
- A feeling of neck pulsations may be due to AV nodal tachycardia caused by simultaneous contraction of atria and ventricles, causing reflux of blood in superior vena cava. Associated "shirt flapping" (visible movement of patient's clothes during the episode) can also be noted in AV node re-entry tachycardia.
- An irregular heartbeat suggests atrial fibrillation.
- The association of polyuria and palpitations may indicate supraventricular tachycardia because increased atrial pressures stimulate production of natriuretic peptides.

Mode of Onset and Termination

- Palpitations that start and terminate abruptly usually indicate atrial or ventricular tachyarrhythmias.
- Palpitations that occur gradually usually indicate benign aetiologies, such as sinus tachycardia during exercise or anxiety.

Precipitating Factors

- A history of palpitations during strenuous activity is often normal, but palpitations during minimal stress suggest an underlying pathology, such as myocardial ischaemia, congestive heart failure, atrial fibrillation, anaemia or thyrotoxicosis.
- Prolonged QT syndrome may present with palpitations during times of catecholamine excess and manifest itself as polymorphic ventricular tachycardia (VT) during these times.
- Use of drugs is another major precipitating cause of palpitations. Although patients may not be taking any pre-scribed medications, it is crucial to ask them if they have taken any over-the-counter remedies (e.g. sympatho-mimetic agents for allergies or colds), diet pills, illicit drugs (e.g. cocaine), alcohol, tobacco, or even caffeinated beverages or chocolate.

Associated Symptoms

- Include syncope, anxiety, dizziness and chest pain.
- Syncope is a serious symptom in patients with palpitations and may represent VT or a very rapid supraventricular tachycardia.
- Palpitations associated with anxiety, a lump in the throat, dizziness, and tingling in the hands and face suggest sinus tachycardia accompanying an anxiety state marked by hyperventilation.
- Palpitations associated with angina may suggest myocardial ischaemia precipitated by increased oxygen demand, secondary to a rapid heart rate.

Relief With Vagal Manoeuvres

- Termination of palpitations with carotid massage or other vagal manoeuvres (e.g. Valsalva manoeuvre) may be effective in patients with supraventricular tachycardia.

Family History

- Family history of sudden cardiac death (e.g. arrhythmogenic right ventricular cardiomyopathy, hypertrophic cardiomy-opathy, prolonged QT interval).

Examination

- Examination is often done during symptom-free period.
- Important signs to look for include features of anxiety (e.g. tremors), abnormal vital signs, pale skin, exophthalmos, goitre, jugular venous distension, carotid bruits, diminished carotid upstroke, heart murmurs, gallops and clicks, wheezes, crepitations, lower extremity oedema and calf tenderness.

Laboratory Studies

- Haemoglobin, serum glucose, electrolytes and thyroid function tests.
- Electrocardiogram—may show bundle branch block, short PR interval, delta waves, prolonged QT interval, ischaemia, chamber enlargement, prior myocardial infarction or other forms of organic heart disease.
- Holter monitoring.
- Exercise electrocardiography may be helpful in patients whose palpitations are precipitated by exercise and who have risk factors for ischaemic heart disease.
- Echocardiography to evaluate for any structural heart disease and assessment of left ventricular function.
- Electrophysiology study (an invasive test of electrical conduction system of heart) in selected patients.

Q. Discuss the differential diagnosis of syncope.

Syncope (Fainting)

- Comprises generalised weakness of muscles, loss of postural tone, inability to stand upright and a loss of consciousness.

Faintness (Pre-Syncope)

- Refers to lack of strength with sensation of impending loss of consciousness.
- "Faintness" reflects the prodromal phase of "fainting" (syncope). The sequence of symptoms includes increasing light headedness, blurring of vision proceeding to blackout, heaviness in the lower limbs progressing to swaying and loss of consciousness.

Mechanism

- Fainting (syncope) is a sudden and brief loss of consciousness and postural tone secondary to hypoperfusion of the brain.
- Cerebral ischaemia may be due to sudden vasodilatation, to a sudden fall in cardiac output or to both simultaneously.

Common Precipitating Causes of Syncope

• Warm environment, hot bath	• Rising after prolonged bed rest
• Post-exercise	• Rapid postural change
• Prolonged motionless standing	• Valsalva
• Large meals (carbohydrate load)	• Alcohol
• Volume depletion	• Medications

Types

Vasovagal Syncope

- Mechanisms include reflex slowing of heart mediated through vagus, and marked fall in arterial pressure and peripheral vascular resistance.
- Causes include emotional stress, warm overcrowded room, sudden pain, mild blood loss, anaemia, fever and fasting.
- Clinical features include a "prodromal phase" characterised by nausea, sweating, yawning, epigastric distress, tachypnoea, weakness and confusion. This is followed by faintness, pallor, coldness of hand and feet, and eventually loss of consciousness. Physical examination reveals tachycardia during prodromal phase and bradycardia later with low blood pressure and weak pulse. Consciousness is regained rapidly without confusion, headache or focal neurologic symptoms, though fatigue is frequent. Convulsions can result if recumbency is prevented.
- Vasovagal syncope is common in the young people.

Cardiac Syncope

- Cardiac syncope is due to a sudden reduction in cardiac output. This can occur when the heart is beating too fast or too slow or when it is not beating at all. It can also occur when there is obstruction to outflow of blood from the heart or cardiac contractility is reduced markedly.
- Common causes of cardiac syncope are given in the information box.

• Complete heart block (Stokes–Adams–Morgagni syndrome)	• Hypertrophic cardiomyopathy (exertional syncope)
	• Primary pulmonary hypertension
• Paroxysmal tachycardias (supraventricular or ventricular)	• Pulmonary embolism
	• Left atrial ball valve thrombus or myxoma
• Sick sinus syndrome	• Tetralogy of Fallot
• Acute massive myocardial infarction	• Long QT syndrome
• Aortic stenosis (exertional syncope)	• Brugada syndrome

Orthostatic Syncope (Postural Syncope)

- This occurs when the person suddenly gets up from a lying down position or stands still for a long time. Basic mechanism is postural hypotension resulting from loss of vasoconstrictor reflexes in the lower limb vessels.
- Common causes of orthostatic hypotension are:
  - Physiological
  - Idiopathic orthostatic hypotension
  - Drugs including antihypertensive drugs

- Diabetic neuropathy and tabes dorsalis
- Haemorrhage

Drug-Induced Syncope

Vasodilators/volume depletion	Arrhythmogenic
- Angiotensin-converting enzyme inhibitors (ACE inhibitors) - β-blockers - Calcium channel blockers - Diuretics	- Quinidine - Amiodarone - Tricyclic antidepressants

Syncope Associated with Cerebrovascular Disease

- Caused by occlusion in the large arteries in the neck.
- Physical activity can further reduce the blood flow (which is already compromised) to the brainstem resulting in loss of consciousness.

Miscellaneous Causes of Syncope

- Carotid sinus syncope (hypersensitive carotid sinus) is common in elderly patients. It follows some form of compression on the carotid sinus as in turning the head to one side, tight collar or shaving over the region of carotid sinus.
- Vagal and glossopharyngeal neuralgia.
- Micturition syncope is seen in elderly patients during or after micturition, particularly after arising from the bed.
- Cough syncope follows paroxysms of cough in elderly patients with chronic bronchitis. During coughing, intrathoracic pressure is elevated, resulting in decreased venous return to the heart, in turn resulting in diminished cardiac output. Diaphragm contraction further impedes venous return by vena cava compression.
- Hyperventilation and hysterical fainting.

Investigations

- Metabolic parameters, particularly blood sugar, sodium and urea
- Electrocardiogram
- Echocardiography
- Holter monitoring (ambulatory ECG)
- Carotid sinus massage
- Electroencephalogram
- Tilt-table test
- CT head

Q. Define cyanosis. Mention the causes and mechanisms of central and peripheral cyanosis.

Q. How will you differentiate central cyanosis from peripheral cyanosis?

Q. Explain in brief about differential cyanosis.

Definition

- Cyanosis is defined as a bluish discolouration of the skin and mucous membranes, resulting from an increased amount of reduced haemoglobin (more than 5 g/dL), or of haemoglobin derivatives in the capillary blood.
- Smaller concentrations of methaemoglobin and sulphmethaemoglobin (1.5 and 0.5 g/dL, respectively) may also evoke cyanosis.
- Cyanosis is most marked in the lips, nail beds, ears and malar eminences.

Types of Cyanosis and their Mechanisms

- Cyanosis can be subdivided into two: Central cyanosis and peripheral cyanosis.
- Central cyanosis is due to decreased arterial oxygen saturation (most of the cases) or the presence of an abnormal haemoglobin derivative (rarely).
- Peripheral cyanosis is due to slowing of blood flow to an area, resulting in greater extraction of oxygen from normally saturated arterial blood. This results from vasoconstriction or diminished peripheral blood flow (reduced cardiac output).

Causes

Central cyanosis	Peripheral cyanosis

• Due to decreased arterial oxygen saturation
  • Cardiac causes
    - Fallot's tetralogy
    - Eisenmenger's syndrome
    - Congestive cardiac failure
  • Pulmonary causes
    - Chronic bronchitis
    - Interstitial lung disease
    - Pulmonary arteriovenous fistula
  • High altitude
  • Cirrhosis of liver
 	
• Due to abnormal haemoglobin derivatives
  • Methaemoglobinaemia
  • Sulphaemoglobinaemia
	• Due to diminished peripheral blood flow resulting from reduced cardiac output
	  • Mitral stenosis
	  • Congestive cardiac failure
	  • Shock
	
	• Due to local vasoconstriction
	  • Cold exposure
	  • Raynaud's disease
	  • Peripheral vascular disease

Differentiation Between Central and Peripheral Cyanosis

Feature	Central cyanosis	Peripheral cyanosis
• Site	Mucous membranes and skin are both involved	Mucous membranes of the oral cavity or those beneath the tongue spared
• Tongue	Affected	Unaffected
• Temperature of limb	Warm	Cold
• Clubbing	Present (shunts)	Absent
• Polycythaemia	Present (shunts)	Absent
• Local warming	Cyanosis remains	Cyanosis disappears
• Breathing pure oxygen for 10 minutes	Cyanosis may disappear	Cyanosis remains
• Arterial blood gas studies	Abnormal	Normal

- Cyanosis in cardiac failure is often of a mixed type due to both central and peripheral causes.
- "Differential cyanosis" is cyanosis occurring in the lower limbs, but not in the upper limbs. This occurs in patients with patent ductus arteriosus with a reversal of shunt.
- Cyanosis of only upper limbs can occur in patients with patent ductus arteriosus with reversal of shunt in combination with transposition of great vessels.
- Cyanosis of left-upper limb and both lower limbs (sparing right upper limb) can occur in patients with patent ductus arteriosus with reversal of shunt in combination with a pre-ductal coarctation of aorta.
- Intermittent cyanosis in Ebstein's anomaly.

Q. Discuss the clinical value of examination of radial and carotid pulses at bedside.

- Study of peripheral arterial pulses include the examination of radial, brachial, carotid, femoral, popliteal, posterior tibial and dorsalis pedis pulses.
- Examination should be performed under the following headings:

• Rate • Rhythm • Volume	• Character or quality • Condition of vessel wall • Radiofemoral delay

- Rate and rhythm are assessed by palpating radial artery.
- Pulse volume is best assessed by palpating carotid artery.
- Pulse character is best assessed by palpating carotid artery except collapsing pulse that is better appreciated at radial artery.

Normal Arterial Pulse Tracing
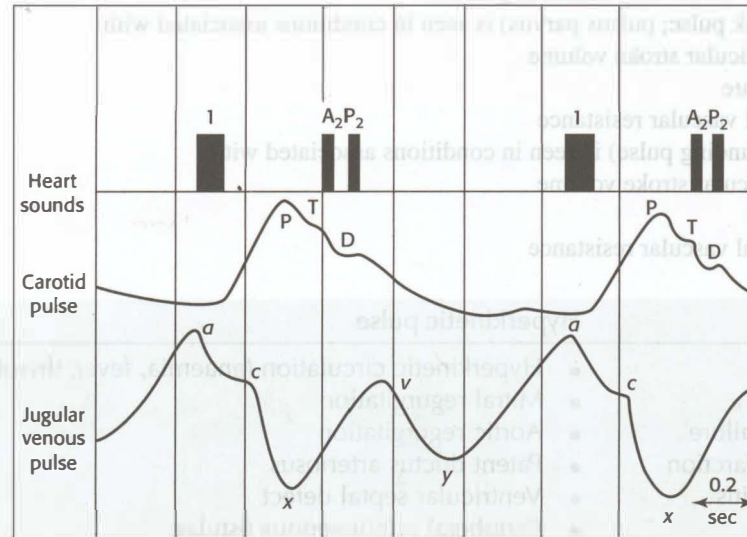
Relationships between the hearts sounds, arterial pulse and jugular venous pulse

1: First heart sound. A$_2$: Aortic component of the second heart sound. P$_2$: Pulmonary component of the second heart sound. P: Percussion wave. T: Tidal wave. D: Dicrotic notch. a, c, x, v and y: Waves and troughs of the jugular venous pulse.

Rate

- Radial pulse is used to assess the rate.
  - Normal—resting pulse rate of 60–100 beats/minute
  - Bradycardia—resting pulse rate less than 60 beats/minute
  - Tachycardia—resting pulse rate more than 100 beats/minute

Bradycardia (less than 60 beats/minute)	Tachycardia (more than 100 beats/minute)
• Athletes	• Anxiety
• Hypothyroidism	• Fever
• Vasovagal syncope	• Pregnancy
• Drugs—β-blockers	• Hyperthyroidism
• Heart block	• Cardiac failure
• Sick sinus syndrome	• Tachyarrhythmias
• Hypothermia	• Drugs—salbutamol, terbutaline

- "Pulse deficit" (apex-pulse deficit)
  - Definition—The difference between the heart rate counted by auscultation and pulse rate is called pulse deficit.
  - Significance—Pulse deficit occurs in atrial fibrillation. Can also occur with multiple ventricular premature beats.
  - Mechanism—Atrial fibrillation is characterised by cycles of varying lengths of diastole. This results in varying stroke volumes with some of the ventricular contractions too weak and unable to open the aortic valve, but at the same time many are good enough to close the mitral valve, thereby producing heart sounds (for further details, refer "atrial fibrillation"). In multiple ventricular premature beats, ectopics beats may not be conducted to radial artery resulting in pulse deficit.

Rhythm

- Radial pulse is used to assess the rhythm.

Completely irregular (irregularly irregular)	Irregularity with a recurring pattern (regularly irregular)
• Atrial fibrillation	
• Frequent extrasystoles	• Sinus arrhythmia
Otherwise regular with occasional irregularity	• Pulsus bigeminus
• Extrasystoles	• Pulsus trigeminus
	• Partial AV blocks

Volume

- Carotid artery is used to assess the volume of pulse.
- Hypokinetic pulse (weak pulse; pulsus parvus) is seen in conditions associated with:
  - Decreased left ventricular stroke volume
  - Narrow pulse pressure
  - Increased peripheral vascular resistance
- Hyperkinetic pulse (bounding pulse) is seen in conditions associated with:
  - Increased left ventricular stroke volume
  - Wide pulse pressure
  - Decreased peripheral vascular resistance

Hypokinetic pulse	Hyperkinetic pulse
- Hypovolaemia	- Hyperkinetic circulation (anaemia, fever, thyrotoxicosis, exercise)
- Shock	- Mitral regurgitation
- Congestive cardiac failure	- Aortic regurgitation
- Acute myocardial infarction	- Patent ductus arteriosus
- Constrictive pericarditis	- Ventricular septal defect
- Mitral stenosis	- Peripheral arteriovenous fistulae
- Aortic stenosis	- Complete heart block

Character or Quality

- Carotid artery is generally used to assess the character of pulse, though sometimes radial artery gives better information.

Pulsus Parvus

- A hypokinetic pulse, which is of low amplitude.
- Occurs as a result of a reduction in left ventricular stroke volume (e.g. congestive heart failure) or a decrease in systemic arterial pressure.

Pulsus Tardus

- A slow rising pulse that peaks late in systole.
- Seen in aortic stenosis.

Pulsus Parvus et Tardus

- Description—This is a small volume ('parvus') pulse that rises slowly 'tardus') to a late systolic peak. There is an associated coarse systolic thrill.
- Mechanism—This is the result of mechanical obstruction to left ventricular ejection.
- Significance—Seen in aortic stenosis.

Anacrotic Pulse

- Description—This is a variant of 'pulsus parvus et tardus', in which a notch is palpable on the upstroke of the pulse wave.
- Significance—Occurs in severe aortic stenosis.

Collapsing (Water–Hammer) Pulse

- Description—This is a pulse characterised by a rapid upstroke, rapid downstroke and a high volume.
- Mechanism—The rapid upstroke is due to the markedly increased stroke volume. The rapid downstroke or the collapsing character is due to two factors:
  - The diastolic leak back into left ventricle.
  - Rapid run-off to the periphery because of low systemic vascular resistance.
- Significance—Collapsing pulse is seen typically in aortic regurgitation. Similar pulse may also be seen in other conditions.

Causes of Collapsing Pulse

- Patent ductus arteriosus
- Ruptured sinus of Valsalva
- Large arteriovenous fistulae
- Truncus arteriosus

- Aortic regurgitation (may not be seen in acute aortic regurgitation)
- Hyperkinetic circulatory states (anaemia, fever, thyrotoxicosis, exercise, pregnancy, Paget's disease, beriberi)
- Mitral regurgitation (occasional)
- Complete heart block (occasional)

- Corrigan's pulse is largely used to describe abrupt distension and quick collapse of carotid pulse whereas the term "water–hammer pulse" is used for the characteristic pulse seen in peripheral arteries like the radial artery.

Bisferiens Pulse

- Description—This is a pulse with double peak (two peaks), both being felt in systole.
- Mechanism—This is due to a combination of the slow rising pulse of aortic stenosis and collapsing pulse of aortic regurgitation.
  - Significance—Bisferiens pulse is seen in the following conditions:
    - Combination of aortic stenosis and aortic regurgitation
    - Severe aortic regurgitation
    - Hypertrophic cardiomyopathy

Dicrotic Pulse

- Description—Dicrotic pulse has two palpable waves, one in systole and other in diastole. Diastolic wave follows dicrotic notch.
- Mechanism—Due to very low stroke volume.
- Significance—Seen in the following conditions:
  - Dilated (congestive) cardiomyopathy
  - Extreme dehydration
  - Advanced cardiac failure
  - Cardiac tamponade

Pulsus Alternans

- Description—This is an alternation of large and small volume beats, with a normal rhythm. There is a difference of 10–40 mmHg in systolic pressure between beats.
- Mechanism—Pulsus alternans is due to alternating left ventricular contractile force, i.e. the ventricle beats strongly, then weakly, alternating with each other.
- Significance—Seen in acute left ventricular failure. It may occur following paroxysmal tachycardia.

Pulsus Bigeminus

- Description—Pulse with regular alteration of pressure pulse amplitude. This is clinically felt as two beats followed by a pause, thereby producing irregular rhythm (in contrast to pulsus alternans where rhythm is regular).
- Mechanism—It is caused by coupled ectopic beats, i.e. an ectopic beat following each regular beat.

Pulsus Paradoxus

- Description—Pulsus paradoxus is characterised by the following features.
  - A decrease in systolic blood pressure more than 10 mmHg during inspiration.
  - A radial pulse that gets smaller in volume (and may even disappear) with inspiration and larger in volume with expiration.
- It is important to note the following points in relation to pulsus paradoxus:
  - A decrease in systolic blood pressure by 3–10 mmHg and a small reduction in the volume of pulse during inspiration are physiological. Pulsus paradoxus is merely an exaggeration of this and NOT a reversal of this.
  - The "paradox" in the pulse is that heart sounds are still audible at a time when no radial pulse is felt.
  - Mild cases of pulsus paradoxus may not alter the radial pulse volume, which may appear normal. But sphygmo-manometric measurement of systolic pressure during slow respiration will detect a more than 10 mmHg fall during inspiration.

Mechanism of Pulsus Paradoxus

- In normal people, during inspiration there is a reduction in intrathoracic pressure, resulting in the following:
  - Pooling of blood in pulmonary vasculature
  - Pooling of blood in the right ventricle due to increased venous return
- This generalised pooling of blood results in a reduction in the venous return to the left atrium and left ventricle. The net result is a reduction in cardiac output resulting in a drop of systolic blood pressure by 3–10 mmHg.
- In pulsus paradoxus, during inspiration the increased right ventricular volume of blood results in a bulging of the interventricular septum into the left ventricular cavity. This results in a reduction in the left ventricular volume leading to a further reduction in cardiac output. This exaggerates the normal inspiratory reduction in blood pressure, allowing it to exceed 10 mmHg. In patients with severe asthma, obstructive airway disease or tension pneumothorax, the degree of negative pressure generated during inspiration is exaggerated. This results in enhanced pooling of blood, thereby causing pulsus paradoxus.

Conditions Associated with Pulsus Paradoxus

- Constrictive pericarditis
- Cardiac tamponade
- Pericardial effusion (rare)
- Restrictive cardiomyopathy
- Chronic obstructive airway disease (severe)
- Severe bronchial asthma
- Tension pneumothorax

Reverse Pulsus Paradoxus

- Indicates inspiratory rise in arterial blood pressure
- Seen in hypertrophic cardiomyopathy, intermittent positive pressure ventilation and AV dissociation

Radiofemoral Delay

- Occurs in coarctation of aorta
- Elicited by simultaneous palpation of right radial artery and one femoral artery
- Features of radiofemoral delay are the following:
  - Femoral pulse is of small volume
  - Femoral pulse occurs after radial pulse
  - Lower limb blood pressures will be lower than upper limb blood pressures.

Pulsus paradoxus
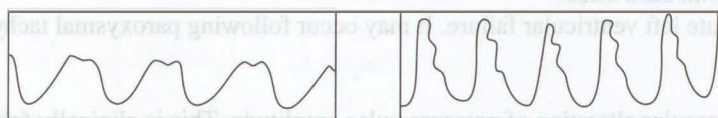
Bisferiens pulse   Collapsing (water-hammer) pulse
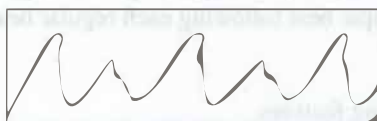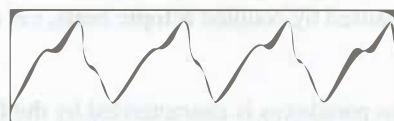
Pulsus bigeminus   Anacrotic pulse
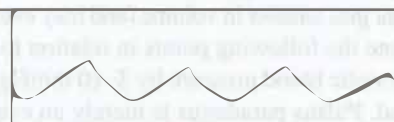
Pulsus alternans   Pulsus parvus et tardus
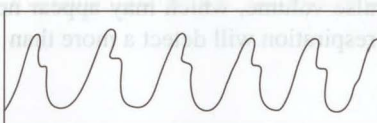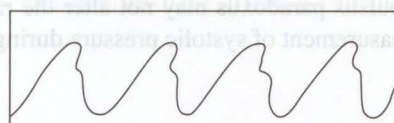
Dicrotic pulse   Normal pulse

Q. Describe the normal wave patterns of JVP and their variations.

Q. How will you differentiate jugular venous pulse from carotid pulse?

Q. Briefly describe hepatojugular reflux and abdominojugular reflux test.

Q. Give a brief account of Kussmaul's sign.

Q. How do you calculate central venous pressure from jugular venous pressure?

Definition

- Jugular venous pulse is the oscillating top of a height of venous blood in the internal jugular vein that faithfully reflects the pressure and haemodynamic changes in the right side of heart in all phases of the cardiac cycle.

Significance

- Two main objectives of examining the JVP (jugular venous pulse) are the following:
  - Estimation of jugular venous pressure
  - Study the waveform

Jugular Venous Pressure

- Jugular venous pressure is expressed as the vertical distance in centimetres between the top of the venous column and the sternal angle, regardless of the body position. Normally, it is less than 3 cm. By convention, jugular venous pressure is measured from the sternal angle with the patient reclining at 45°.
- Central venous pressure can be accurately estimated from the jugular venous pressure. For this, the sternal angle is taken as the reference point. The centre of the right atrium lies 5 cm below the sternal angle, regardless of body position. The central venous pressure is calculated as 5 + jugular venous pressure in centimetres (e.g. if jugular venous pressure is 6 cm, the central venous pressure = 5 + 6 = 11 cm of blood).
- In other words, jugular venous pressure reflects the central venous pressure and also the mean right atrial pressure.

Normal Wave Patterns of Jugular Venous Pulse
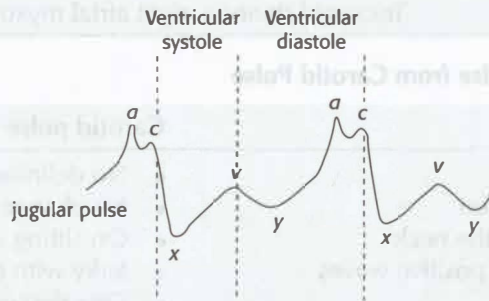
a: Atrial contraction. c: Onset of ventricular contraction. v: Pressure peak immediately prior to opening of tricuspid valve. c–x : x descent. v–y : y descent

- The various waves on JVP reflect the phasic pressure changes in the right atrium.
- Normal JVP has three positive waves, namely, a, c and v waves, and two negative descents namely x descent and y descent.
- In normal persons, the a wave is more visible than the v wave, and the x descent is more prominent than the y descent. In fact, the v wave and y descent are often not visible in healthy adults owing to the very compliant normal right atrium.

Mechanism

- The a wave is due to right atrial contraction. It occurs just before the first heart sound and before the onset of ventricular ejection (carotid pulse upstroke).
- The c wave is due to bulging of the tricuspid valve into the right atrium and impact of the adjacent carotid artery during ventricular systole.
- The v wave is due to passive right atrial filling during ventricular systole.
- The x descent ("systolic collapse") is due to atrial relaxation and downward displacement of tricuspid valve during systole. It occurs during systole and ends just prior to second heart sound.
- The y descent ("diastolic collapse") is due to opening of the tricuspid valve and the rapid flow of blood into the right ventricle. It occurs after second heart sound.

Abnormalities in Jugular Venous Pressure

Causes of Raised Jugular Venous Pressure

- Right heart failure (commonest)
- Tricuspid regurgitation
- Tricuspid stenosis
- Pulmonary embolism
- Overuse of IV fluids

- Constrictive pericarditis
- Cardiac tamponade
- Superior vena caval obstruction (non-pulsatile)
- Acute nephritis
- Massive ascites or right-sided pleural effusion

Abnormalities in Wave Form

Abnormalities	Conditions
• Abnormalities of the *a* wave	
• Large *a* waves	Tricuspid stenosis, pulmonary hypertension, pulmonary stenosis, right ventricular hypertrophy
• Regular "cannon" *a* waves	Junctional rhythm
• Irregular "cannon" *a* waves	Complete heart block, multiple ectopics
• Absent *a* waves	Atrial fibrillation
• Abnormalities of the *v* wave	
• Large *v* waves	Tricuspid regurgitation, right ventricular failure
• Abnormalities of the *x* descent	
• Increased prominence	Cardiac tamponade, constrictive pericarditis, atrial septal defect
• Decreased prominence	Tricuspid regurgitation (replaced by *c–v* wave), right ventricular failure, atrial fibrillation
• Abnormalities of the *y* descent	
• Rapid *y* descent	Tricuspid regurgitation, restrictive heart disease including constrictive pericarditis, severe right heart failure
• Slow *y* descent	Tricuspid stenosis, right atrial myxoma, cardiac tamponade

Differentiation of Jugular Venous Pulse from Carotid Pulse

Jugular venous pulse	Carotid pulse
• Definite upper level	• No definite upper level
• Upper level falls during inspiration	• No change with respiration
• On sitting up, appears lower in the neck	• On sitting up, appears higher in the neck
• Wavy column with two to three positive waves	• Jerky with only one wave
• Two descents (*x* and *y*)	• One descent
• Not palpable or palpable as a slight fluttering sensation	• Well palpable as a pulsation
• Obliterated by mild pressure at root of neck	• Not obliterated by pressure at root of neck
• Hepatojugular reflux present	• Hepatojugular reflux absent

Hepatojugular Reflux (Abdominojugular Reflux Test)

- Procedure—The palm of the hand is placed over the abdomen in periumbilical area and firm pressure is applied for a minimum period of 10 seconds, ensuring that the patient does not perform a Valsalva manoeuvre.
- Normal response—The upper level of jugular venous pulsation moves upwards by less than 3 cm and then falls down even when the pressure is continued.
- Positive abdominojugular reflux test—It is defined as an increase in JVP (more than 3 cm) during 10 seconds of firm mid-abdominal compression, remains high throughout the period of compression, followed by an abrupt drop in pressure of 4 cm of blood upon release of compression.
- Clinical significance
  - It is positive in early or incipient right heart failure.
  - Abdominojugular reflux test is positive in right heart failure, secondary to elevated left heart filling pressures.
  - With hepatojugular reflux, the typical JVP of tricuspid regurgitation can be elicited even when the resting pulse wave is normal.

- During abdominojugular reflux testing, the upper level of JVP does not move upward at all in inferior vena caval obstruction and Budd–Chiari syndrome (hepatic vein occlusion).

Kussmaul's Sign

- Normally, there is a decrease in the height of jugular venous pulsations and a drop in jugular venous pressure during inspiration.
- Kussmaul's sign is an increase in the height of jugular venous pulsations and hence a rise in jugular venous pressure (central venous pressure) during inspiration.
- Kussmaul's sign is seen in the following conditions:
  - Constrictive pericarditis
  - Restrictive cardiomyopathy
  - Severe right-sided heart failure
  - Right ventricular infarction
  - Acute severe asthma
  - Pulmonary embolism

Q. Discuss the clinical importance of apex beat.

Q. Define apical impulse and discuss the abnormalities of apical impulse.

Definition

- Apex beat is the lowermost and outermost point of definite cardiac pulsation.
- Also known as "point of maximum impulse".

Normal Apex Beat

- Left ventricle normally produces the apex beat.
- Site of the apex beat
  - With the patient in supine or sitting posture, it is located 1 cm medial to the midclavicular line or 9–10 cm from the midsternal line, in the fifth left intercostal space.
  - With the patient lying on his left lateral side, the apex beat may move 1–2 cm laterally.
- Features of the normal apex beat
  - It is palpable only during the first half of systole and lasts less than 30% of systole. On palpating the carotid artery simultaneously, the apical beat does not last longer than the carotid upstroke.
  - It gently raises the palpating finger.
  - It is detectable in only one intercostal space and is less than 3 cm in diameter.

Abnormalities of Apical Impulse

- Abnormalities in character
- Abnormalities in position

Abnormalities in Character

- Hyperdynamic apex
- Heaving apex
- Tapping apex
- Hypokinetic apex
- Double apex

Hyperdynamic Apex (Hyperkinetic Apex; Volume Overload Apex; Diffuse Apex; Forceful and Ill-Sustained Apex)

- Site of the apex beat
  - Shifted downwards and laterally due to chamber enlargement resulting from volume overload
- Features of the hyperdynamic apex beat:
  - The apical thrust is increased in amplitude.
  - It lifts the finger up, but the lift is not sustained.
  - It lasts more than 30% but less than 60% of systole.
  - It is detectable in more than one intercostal space and is more than 3 cm in diameter.

- Conditions associated with hyperdynamic apex beat:

Increased left ventricular stroke volume (volume overload)	Dilated cardiomyopathy
	Hyperdynamic circulatory states
• Aortic regurgitation	• Exercise
• Mitral regurgitation	• Thyrotoxicosis
• Ventricular septal defect	• Severe anaemia
• Patent ductus arteriosus	

Heaving Apex (Sustained Apex; Pressure Overload Apex; Forceful and Sustained Apex)

- Site of the apex beat
  - Usually normal in position and results from left ventricular hypertrophy due to pressure overload.
- Features of the heaving apex beat
  - The apical thrust is increased in amplitude and duration.
  - The duration of the thrust is prolonged and felt in the second half of systole also.
  - It lasts more than 60% of systole.
  - It lifts the finger up and the lift is sustained.
  - It is detectable in only one intercostal space and is less than 3 cm in diameter.
- Conditions associated with heaving apex beat (pressure overload of left ventricle):

• Aortic stenosis	• Coarctation of aorta
• Systemic hypertension	• Hypertrophic cardiomyopathy

Tapping Apex

- It is due to palpable loud first heart sound.
- It imparts a tapping feeling to the palpating finger.
- Occurs in mitral stenosis.

Hypokinetic Apex or Absent Apical Impulse

• Obesity	• Pericardial effusion	• Shock
• Emphysema	• Constrictive pericarditis	• Myxoedema

Double Apex

- Occurs in hypertrophic cardiomyopathy and left ventricular aneurysm.

Abnormalities in Position — Causes

Cardiac enlargement	Cardiac displacement	Dextrocardia
• Aortic regurgitation	• Scoliosis, funnel chest	
• Mitral regurgitation		**Pleural diseases**
• Ventricular septal defect	**Pulmonary diseases**	• Pleural effusion
• Patent ductus arteriosus	• Pulmonary fibrosis	• Pneumothorax
• Dilated cardiomyopathy	• Collapse of lung	• Hydropneumothorax
	• Large pulmonary masses	• Pleural fibrosis

Q. Briefly discuss about parasternal heave or parasternal impulse.

- Indicates forward (anterior) movement of lower left parasternal area.
- Palpated with the base or ulnar aspect of hand.
- Three grades.
  - Grade 1: Visible impulse but not palpable.
  - Grade 2: Visible and palpable but obliterable with pressure.
  - Grade 3: Visible and palpable but not obliterable with pressure.
- Seen in right ventricular enlargement (as in atrial septal defect, ventricular septal defect, pulmonic stenosis, pulmonary hypertension) and left atrial enlargement.

Q. What is the mechanism of first heart sound? Discuss the variations in first heart sound.

- The first heart sound (S_1) results from the closure of mitral and tricuspid valves. It has two components:
  - Mitral component (M_1) due to mitral valve closure
  - Tricuspid component (T_1) due to tricuspid valve closure
- The mitral component (M_1) is followed by the tricuspid component (T_1).
- Splitting of S_1 is usually not heard because the sound of tricuspid valve closure is too faint to hear.
- S_1 is best heard at the apex. It is best heard with the diaphragm of stethoscope.
- Intensity of S_1 is determined primarily by valve mobility, force of ventricular contraction, and most importantly, the velocity of valve closure. S_1 is louder when onset of ventricular systole finds mitral leaflets still widely open such as in mitral stenosis with pliable leaflets, a short PR interval, tachycardias and increased diastolic flow rates. Alternatively, a soft S_1 occurs when the AV valves are partially closed at the onset of ventricular contraction, as with a long PR interval, acute aortic regurgitation and decreased flow rates (low cardiac output).

Variations in the Intensity of First Heart Sound

Loud first heart sound	Soft first heart sound
- Mitral stenosis	- Mitral regurgitation
- Short P–R interval	- Calcified mitral valve
- Hyperdynamic circulatory states	- Long P–R interval
- Exercise	- Myocarditis
- Anaemia	- Left ventricular failure
- Fever	- Severe or acute aortic regurgitation
- Thyrotoxicosis	- Left bundle branch block
- Paget's disease	- Obesity
- Pregnancy	- Emphysema
- Beriberi	- Pericardial effusion
- Left atrial myxoma	**Varying intensity of first heart sound**
- Tricuspid stenosis	- Atrial fibrillation
- Thin chest wall	- Complete AV block
	- Ventricular tachycardia

Abnormalities in Splitting of First Heart Sound

Wide splitting of first heart sound	Reversed splitting of first heart sound
- Ebstein's anomaly	- Complete left bundle branch block
- Complete right bundle branch block	- Severe mitral stenosis
- Ectopic beat from left ventricle	- Left atrial myxoma
	- Right ventricular pacing
	- Ectopic beat from right ventricle

Q. What is the mechanism of second heart sound? Discuss the variations in second heart sound.

- The second heart sound (S_2) is due to the closure of aortic and pulmonary valves. It has two components:
  - Aortic component (A_2) due to aortic valve closure.
  - Pulmonary component (P_2) due to pulmonary valve closure.
- The aortic component (A_2) is followed by the pulmonary component (P_2).
- Normally, during expiration, both valves close almost simultaneously, and hence, second heart sound is single. During inspiration, the aortic valve closes early due to increased capacitance of pulmonary vascular bed while pulmonary wall closes late due to increase in right ventricular volume. This results in a physiological inspiratory splitting of second heart sound.
- Loudness of A_2 or P_2 is proportional to the respective pressures in aorta or pulmonary artery at the onset of diastole.

Variations in the Intensity of Second Heart Sound

Aortic component (A$_2$)	Pulmonary component (P$_2$)

• Increased intensity
  • Essential hypertension
  • Syphilitic aortic regurgitation
  • Hyperdynamic circulatory states
• Decreased intensity
  • Aortic stenosis
  • Aortic regurgitation
	• Increased intensity
	  • Pulmonary hypertension
	  • Pulmonary artery dilatation
	• Decreased intensity
	  • Pulmonary stenosis
	  • Tetralogy of Fallot
	  • Pulmonary atresia

Abnormalities in Splitting of Second Heart Sound

Wide mobile split	Reversed (paradoxical) splitting

• Delayed electrical activation of right ventricle:
  • Right bundle branch block
  • Ectopic from left ventricle
• Prolonged right ventricular systole
  • Pulmonary stenosis
  • Pulmonary hypertension
  • Massive pulmonary embolism
• Early aortic closure
  • Mitral regurgitation
	• Delayed electrical activation of left ventricle:
	  • Left bundle branch block
	  • Ectopic from right ventricle
	• Prolonged left ventricular systole
	  • Hypertension
	  • Severe aortic stenosis
	  • Hypertrophic cardiomyopathy
	  • Patent ductus arteriosus
	  • Severe left ventricular dysfunction
	  • Early pulmonary valve closure
	    • Tricuspid regurgitation
	• Early electrical activation of right ventricle
	  • Wolff–Parkinson–White syndrome (type B)

Wide fixed splitting	Single second heart sound
• Atrial septal defect • Severe pulmonary stenosis • Severe right ventricular failure	• Severe aortic stenosis (absent or markedly attenuated A$_2$) • Severe pulmonary stenosis (absent or markedly attenuated P$_2$) • Tetralogy of Fallot

Q. Discuss the significance of third heart sound.

- Third heart sound (S$_3$) is produced in the ventricle due to abnormal filling pattern. It is a low-pitched sound heard at the end of rapid filling phase (early diastole). It occurs 0.14–0.22 seconds after the second heart sound.
- A third heart sound arising from the left ventricle is known as "left-sided third heart sound" and the one arising from right ventricle as "right-sided third heart sound".
- S$_3$ is best heard with the bell of stethoscope.
- Left-sided S$_3$ is best heard during expiration with the patient in the left lateral position.
- Right-sided S$_3$ is best heard during inspiration.
- Left-sided S$_3$ may be physiological or pathological. Right-sided S$_3$ is always pathological.

Causes of Third Heart Sound

Physiological S$_3$	Hyperdynamic states	Pathological left-sided S$_3$	Pathological right-sided S$_3$
• Children • Under 40 years • Athletes • Pregnancy	• AV fistula • Thyrotoxicosis	• Left ventricular failure • Aortic regurgitation • Mitral regurgitation • Ischaemic heart disease • Cardiomyopathy	• Right ventricular failure

Q. Discuss the significance of fourth heart sound.

- Fourth heart sound (S$_4$) occurs as a result of forceful atrial contraction ("atrial kick"). It is a low-pitched sound heard in pre-systole (late diastole; before first heart sound). It is absent in atrial fibrillation.

- S_4 may be confused with spilt S_1. Firm pressure by the diaphragm of stethoscope eliminates S_4 but not split S_1.
- S_4 is always abnormal.
- A fourth heart sound arising from the left side is known as "left-sided fourth heart sound" and the one arising from right side as "right-sided fourth heart sound".
- Left-sided S_4 is best heard during expiration with the patient in the left lateral position.
- Right-sided S_4 is best heard during inspiration.

Causes of Fourth Heart Sound

Left-sided S_4	Right-sided S_4
• Systemic hypertension	• Right ventricular hypertrophy due to
• Hypertrophic cardiomyopathy	• Pulmonary hypertension
• Ischaemic heart disease (especially acute myocardial infarction)	• Pulmonary stenosis
• Acute mitral regurgitation	
• Anaemia, thyrotoxicosis and AV fistulae	

Q. What is summation gallop?

- It occurs when both S_3 and S_4 are present in a patient with tachycardia.
- Due to shortening of diastole, the two sounds (S_3 and S_4) merge to produce a single loud sound.

Q. Discuss other cardiac sounds on auscultation.

Ejection Click

- Ejection click is a sharp, high-frequency sound audible immediately after S_1. It can occur with aortic valve stenosis, pulmonary valve stenosis as well as in dilation of ascending aorta and pulmonary artery.
- An aortic ejection click is audible over the entire precordium and varies little with respiration. A pulmonary click is most audible along the left-upper sternal border, becoming louder during expiration and less audible or absent during inspiration.
- As the valves become stiff and calcified in aortic and pulmonary stenosis, ejection click disappears.

Non-Ejection Click

- Associated with mitral valve prolapse.
- High-frequency, sharp clicks occurring over the apex or left-lower sternal border.
- May be an isolated finding or be followed by late systolic murmur.
- Manoeuvres such as squatting move a midsystolic click towards S_2, whereas standing and performing the Valsalva manoeuvre move the click towards S_1.
- Midsystolic click arises from sudden tension on the chordae tendineae or from sudden halt of prolapsing mitral valve leaflet during ventricular systole.

Prosthetic Valve Sounds

- A ball-in-cage prosthesis (Starr–Edwards) has loud, clicking opening and closing sounds. In the case of aortic valve, opening sound has the same timing as an ejection sound (ES), and in the case of the mitral valve it occurs when an opening snap (OS) would occur. Closing sound corresponds to the component of the heart sounds contributed by that valve, i.e. mitral component of S_1 for mitral valve and aortic component of S_2 for an aortic valve.
- Disc valves produce distinct closing sounds but usually no audible opening sounds.
- Tissue valves do not normally produce additional sounds.

Q. Discuss the conduction system of the heart briefly.

- The rate and rhythm of the heart are controlled by the sinoatrial node (SA node) situated at the junction of superior vena cava and right atrium.
- The impulse from the SA node spreads through the atrial musculature and down to the atrioventricular (AV) node that is situated above the tricuspid valve.
- Passage through the AV node is relatively slow, accounting for the normal physiological delay in ventricular depolarisation.

- The impulse then travels downwards to the bundle of His and through its branches (right bundle branch and left bundle branch) to the Purkinje network of fibres that convey the impulse to the ventricular endocardium and then epicardium.
- The SA node is the normal pacemaker of the heart as it has the fastest inherent discharge rate. However, potential pace-making properties also exist in the cells of the AV node, bundle of His and Purkinje fibres.

Q. How do you analyse an electrocardiogram?

Rate

- The ECG is normally recorded at a speed of 25 mm/second so that each small square, i.e. 1 mm represents 0.04 seconds.
- The atrial and ventricular rates are calculated by counting the number of small squares between two consecutive P waves (P–P interval) and R waves (R–R interval), respectively. Dividing 1500 by P–P and R–R intervals gives the atrial and ventricular rates, respectively.
- Though normally both atrial and ventricular rates are equal, they should be calculated separately since they can be different in complete AV block and paroxysmal supraventricular tachycardia (PSVT) with 2° AV block.
- A heart rate >100/minute is tachycardia and <60/minute is bradycardia.

Rhythm

- See whether it is regular or irregular. If there is any doubt, use a piece of paper to map out three or four consecutive beats and see whether rate is same further along the ECG.
- Check for: P wave before each QRS complex, PR intervals (for AV blocks) and QRS interval (for bundle branch block).

Regular Rhythm

- In sinus rhythm, P wave precedes every QRS complex with consistent P–R interval.
- In nodal or junctional rhythm no discernable P wave preceds each QRS complex; the QRS complexes are narrow and regular with constant R–R interval.

Irregular Rhythm

- In atrial fibrillation no discernable P waves preced each QRS complex; the QRS complexes are irregular with varying R–R intervals.
- Irregular rhythm with P wave preceding each QRS with consistent P–R interval is sinus arrhythmia.
- Premature beats—After a premature beat the atria and the ventricles are in a refractory state, and hence, the next expected sinus impulse is blocked. This produces a pause that is known as compensatory pause. It is called complete when the duration of R–R interval, including the premature beat is twice that of the normal R–R interval, and incomplete when it is less than twice the duration of normal R–R interval. Incomplete compensatory pause is a feature of supraventricular premature beats whereas complete compensatory pause is seen in ventricular premature beats.

Abnormalities in Irregular Rhythm

Irregularly irregular rhythm	Regularly irregular rhythm

- Atrial fibrillation
- Multiple premature beats
  - Complete compensatory pause:
    - Ventricular premature beats
  - Incomplete compensatory pause:
    - Supraventricular premature beats
- Sinus arrhythmia
	- Complete compensatory pause:
	  - Ventricular premature beats
	- Incomplete compensatory pause:
	  - Supraventricular premature beats
	- 2° AV block of varying type

Axis

- Generally, the axis of leads I and aVF is used to calculate the axis of QRS complex. For this, net deflection of QRS in each lead is calculated by subtracting deflection of Q wave from deflection of R wave (e.g. if in lead I, Q wave measures three small squares and R wave height is six small squares, the net deflection is +3).
- The normal QRS axis is −30° to +110°.
- Left axis deviation (LAD) is an axis between −30° and −90°.
- An axis between +110° and +180° indicates right axis deviation (RAD).

Causes of Axis Deviation

Left axis deviation (LAD)	Right axis deviation
• Left bundle branch block	• Right ventricular hypertrophy
• Left anterior hemiblock	• Chronic obstructive airway disease
• Myocardial infarction	• Left posterior hemiblock
• Hypertrophic cardiomyopathy	
• Left ventricular hypertrophy	
• Wolff–Parkinson–White syndrome	

P Wave

- P wave represents atrial depolarisation. Normally, its duration is <0.1 seconds (<2.5 small squares) and its amplitude is less than 2.5 mm.
- P waves are absent in atrial fibrillation and before ventricular premature beats.
- Normally, all P waves are followed by QRS complexes. In third degree AV block, P waves do not bear any relation to QRS complexes.
- Morphology and duration of P waves are important to determine left and right atrial hypertrophy.
  - A tall P wave >2.5 mm in amplitude (P pulmonale) seen in right atrial enlargement.
  - A wide P wave >0.1 seconds (P mitrale) seen in left atrial enlargement.

P–R Interval

- The P–R interval (normally 0.12–0.20 seconds) reflects intra-atrial, AV nodal and His–Purkinje conduction. It is the interval between the beginning of P wave and the beginning of QRS complex.

Abnormalities in P–R Interval

Prolongation of P–R interval (first degree AV block)	Short P–R interval
• Rheumatic fever (carditis)	• Wolff–Parkinson–White syndrome
• Ischaemic heart disease	• AV nodal rhythm
• Digitalis effect	• Supraventricular tachycardia
	Progressive prolongation of P–R interval
	• Wenckebach's second degree block

QRS Complex

- The QRS complex, representing ventricular depolarisation, has a normal duration of 0.04–0.10 seconds.
- Abnormal Q waves are present in myocardial infarction.
- Wide and bizarre QRS complexes are seen in ventricular ectopics, ventricular tachycardia and supraventricular tachycardia with aberrant conduction.
- Increase in the height of QRS complexes indicates right or left ventricular hypertrophy.
- Left ventricular hypertrophy
  - Sum of S wave in lead V_1 and R wave in lead V_5 or V_6 >35 mm
  - S wave in V_1 >25 mm or R wave in V_5 or V_6 >25 mm
  - R wave in lead aVL >12 mm
  - In systolic overload, q waves in leads I, aVL, V_5 and V_6 may disappear, ST become depressed and T wave becomes inverted.
  - In diastolic overload, q waves become deep in leads I, aVL, V_5 and V_6, and T waves become tall in V_5–V_6.
- Right ventricular hypertrophy
  - Right axis deviation
  - Predominant R wave in V_1 and V_2 (R:S ratio >1) or R wave >5 mm in V_1
  - Sum of R wave in V_1 or V_2 and S wave in V_5 or V_6 >10 mm

Causes of Tall R Waves in V_1

• Right ventricular hypertrophy	• Dextrocardia
• Right bundle branch block	• Hypertrophic cardiomyopathy
• Wolff–Parkinson–White syndrome (type A)	• Posterior wall myocardial infarction

ST Segment

- ST segment elevation or depression is seen in ischaemic heart disease, cardiomyopathies, myocarditis and conduction blocks.
- Some drugs like digitalis can also produce ST segment depression.

T Waves

- T waves represent ventricular re-polarisation.
- Inverted T waves are frequently seen in cases with ischaemic heart disease, bundle branch blocks, atrial fibrillation with rapid ventricular rate and in PSVT (due to relative coronary insufficiency).
- A tall, peaked T wave is seen in hyperkalaemia.

QT Interval

- From beginning of QRS complex to end of T wave
- Corrected QT interval (QT_c) is calculated using the following formula:

$$QT_c = QT/\sqrt{RR}$$

- QT_c >0.45 is abnormal that can be seen in hypokalaemia, hypocalcaemia and congenital QT prolongation syndrome.
- Prolonged QT_c interval may produce torsades de pointes and sudden death.
- QT_c below 0.32 may also predispose to cardiac arrhythmias and sudden death (short QT syndrome).

Q. Explain the usefulness of electrocardiogram.

- Electrocardiography is useful in the following situations:
  - Myocardial ischaemia and infarction
  - Cardiac arrhythmias
  - Conduction defects
  - Chamber (atrium or ventricle) hypertrophy
  - Electrolyte abnormalities (hypokalaemia, hyperkalaemia, hypocalcaemia, hypercalcaemia)
  - Effects of drugs (digitalis)
  - Hypothermia
  - Pericarditis

Q. Define and classify cardiac arrhythmias.

- Any abnormal alteration in either rate or rhythm of cardiac contraction is termed as cardiac arrhythmia.

Classification

Disturbances of impulse formation	Disturbances of impulse conduction

- Disturbances of sinus mechanism
  - Sinus tachycardia
  - Sinus bradycardia
  - Sinus arrhythmia
- Disturbance of atria
  - Atrial premature contraction
  - Atrial fibrillation
  - Atrial flutter
  - Paroxysmal supraventricular tachycardia (PSVT)
- Disturbance of atrioventricular (AV) node
  - Junctional ectopics
  - Junctional rhythm
  - Junctional tachycardia
- Disturbance of ventricles
  - Ventricular ectopics
  - Ventricular tachycardia
  - Ventricular fibrillation (VF)
	- Sinoatrial blocks
	- AV nodal blocks
	  - First degree block
	  - Second degree block
	    - Wenckebach (Mobitz type 1) block
	    - Mobitz type II block
	  - Complete or third degree block
	- Bundle blocks
	  - Right bundle branch block
	  - Left bundle branch block
	  - Left anterior hemiblock
	  - Left posterior hemiblock

Q. Explain sinus arrhythmia.

- Definition—This is a phasic alteration in the heart rate in relation to breathing. The heart rate increases in inspiration and decreases in expiration.
- Significance—This is the most common arrhythmia. It is a normal phenomenon and is a manifestation of normal autonomic nervous activity.

Q. What are ectopic beats (extrasystoles; premature beats)?

Q. Describe supraventricular ectopics (atrial ectopics; atrial premature beats).

Q. Explain briefly about ventricular ectopics (ventricular extrasystoles; ventricular premature beats, premature ventricular contractions—PVC).

Ectopic Beats (Extrasystoles; Premature Beats)

- Definition—A heart beat occurring as a result of an impulse originating in an area other than the sinoatrial (SA) node is known as an ectopic beat.
- Classification—Ectopic beats are classified based on the origin of the impulse (ectopic focus).
  - Supraventricular
    - Atrial (arising from atrium)
    - Junctional (arising from AV junction)
  - Ventricular
- Haemodynamics—An ectopic impulse occurs in diastole. The normal sinus impulse (arising from SA node) following an ectopic impulse will find the ventricles refractory, and hence, not conducted into the ventricles, resulting in a "missed" or "dropped" beat. This is responsible for the "compensatory pause". Compensatory pause allows more filling of the ventricles, and hence, the subsequent beat is more forceful.
- Symptoms include extra beats, thumping beats or missed beats.
- Signs include irregularity in rhythm, missing of beats, post-ectopic bounding beat and cannon waves on JVP.

Supraventricular Ectopics (Atrial Ectopics; Atrial Premature Beats)

- Causes
  - Idiopathic in healthy people
  - Anxiety
  - Excessive coffee, tea or tobacco
  - Ischaemic heart disease
  - Valvular heart diseases
- Electrocardiogram
  - The ECG shows an abnormal P wave (P' wave) that occurs early in the cardiac cycle. Sometimes, it may get buried in the preceding T wave. It may be inverted if the source of its origin is near the AV node.
  - R–R interval preceding and following the ectopic beat is less than twice the basal R–R interval, i.e. the pause following the ectopic is not fully compensated.
  - Most often, the QRS complex is narrow and identical to the sinus rhythm. However, occasionally, P' is conducted aberrantly that results in a wide QRS complex. This must be distinguished from ventricular ectopic beat.
- Treatment
  - Treatment is that of the underlying cause
  - Supraventricular ectopics can sometimes precipitate atrial tachycardia, flutter and fibrillation.

Ventricular Ectopics (Ventricular Extrasystoles; Ventricular Premature Beats)

- Causes

- Idiopathic in healthy people	- Myocarditis
- Excessive tea, coffee and alcohol	- Digitalis toxicity
- Acute myocardial infarction	- Hypokalaemia
- Myocardial ischaemia	- Mitral valve prolapse

- Electrocardiogram
  - A PVC is characterised on the ECG by a wide, bizarre QRS complex, more than 0.12 seconds in duration and usually without a preceding P wave.

- Due to abnormal re-polarisation, PVC is associated with secondary T wave changes that include widening of T wave and deflection of T wave opposite to that of ectopic QRS complex.
- The pause is fully compensated so that the sum of R–R intervals preceding and following the ectopic QRS equals double the normal sinus R–R interval.
- When a PVC depolarises the ventricles at a similar time as a conducted atrial beat, a fusion beat is seen.
- Ventricular bigeminy is present when a ventricular premature beat follows each sinus beat.
- Ventricular trigeminy is present when two sinus beats are followed by the ventricular premature beat. Thus, every third beat is a ventricular premature beat.
- Treatment
  - Treat the underlying cause
  - In the absence of ischaemia, PVCs alone rarely require any specific pharmacologic therapy.
  - In ischaemic heat disease lignocaine may be required if the PVCs are multiform, couplets (two consecutive PVCs) are present, or R-on-T phenomenon (occurrence of PVC on the preceding T wave) is present.
  - Symptomatic healthy people can be treated with β-blockers, amiodarone, disopyramide or mexiletine.

Q. Describe briefly about tachycardias.

Q. Write a brief note on narrow-complex and wide-complex tachycardias.

- Tachycardias are defined as a heart rate >100/minute.
- Tachycardias that utilise atrial or AV nodal tissue as part of their mechanism (i.e. arising above the Bundle of His) are known as supraventricular tachycardia while those below as ventricular tachycardia.
- Another way to classify tachycardias is narrow-complex (QRS complex <0.12 seconds) and wide-complex (QRS >0.12 seconds) tachycardias.
- In general, tachycardias that originate below the AV node produce wide QRS complexes while those originating from or above AV node produce narrow QRS complexes.
- Common causes of wide complex tachycardias include:
  - Ventricular tachycardia
  - Pacemaker-mediated tachycardia
  - Some cases of supraventricular tachycardia (see below)
  - Toxicity of certain medications (e.g. tricyclic antidepressants, diphenhydramine, cocaine)
  - Post-resuscitation cardiac rhythm
  - Hyperkalaemia (usually produces wide-complexes with bradycardia)
- Sometimes, supraventricular and nodal tachycardias may produce widened QRS complexes due to:
  - Antegrade conduction from the atria to the ventricles via an accessory pathway (bundle of Kent and others)
  - Underlying pre-existing bundle branch block
  - Rate-related bundle branch block induced by the tachycardia itself
- Wide complex tachycardia (QRS duration >0.12 seconds), thus, may be either supraventricular or ventricular in origin and differentiation between them is important from the therapeutic point of view.
- Look for any evidence of haemodynamic instability before attempting to differentiate these two types of tachycardia.
- In evaluating a patient with a regular wide complex tachycardia the operating assumption must be that the tachycardia is of ventricular origin until proved to be otherwise.
- ECG criteria that suggest a ventricular tachycardia are listed in the box.

- Presence of fusion beats
- Presence of AV dissociation
- Presence of capture beats
- QRS width >0.14 seconds if RBBB is present or >0.16 seconds if LBBB is present
- QRS axis <−90° to ± 180°
- Pre-cordial concordance

- RBBB pattern with
  - Rsr′ or RS pattern in lead V_1
  - R/S <1 or QS pattern in V_6
- LBBB pattern with
  - Q in V_6
  - Notched downstroke S wave in V_1
  - R >0.03 seconds in V_1

- Capture beats are QRS complexes resulting from ventricular activation originating in supranodal tissue, using electrical conduction pathways above the ventricle. These are therefore narrow and are similar to a normal QRS complex.

- Fusion beats are hybrid QRS complexes and result from simultaneous activation of ventricles via normal conduction through AV node and through ventricular rhythm. They are therefore intermediate in morphology and width from either a capture or ventricular beat.
- Pre-cordial concordance means that QRS direction on the ECG in all the pre-cordial leads is consistent, i.e. all are either positive or negative. Positive pre-cordial concordance, however, may also occur during supraventricular tachycardia with aberrant conduction. Negative pre-cordial concordance nearly always indicates ventricular tachycardia.
- After termination of tachycardia the ECG should be analysed during sinus rhythm for any evidence of QT prolongation, Brugada phenotype, ischaemic heart disease, pre-excitation or an underlying cardiomyopathy; all of these features increase the probability of life-threatening arrhythmias.

Q. What do you understand by the term supraventricular tachycardias? Name various supraventricular tachycardias.

Q. What do you understand by the term "re-entry" arrhythmias.

- Supraventricular tachycardia refers to an arrhythmia having three or more complexes at rates exceeding 100 beats/minute and originating above the ventricle (i.e. either in the SA node, atria or in the AV junction).
- Supraventricular tachycardia includes the following conditions:
  - Sinus tachycardia
  - Atrial fibrillation
  - Atrial flutter
  - Multifocal atrial tachycardia
  - Paroxysmal supraventricular tachycardia (PSVT)
  - Wolff–Parkinson–White syndrome
  - Junctional tachycardia

Re-Entry

- The most common mechanism of arrhythmias is re-entry. This is particularly true for PSVT.
- Re-entry requires presence of two electrophysiologically distinct pathways around an insulated core (e.g. the AV valve annulus).
- In PSVT, re-entry occurs due to presence of an additional electrical connection between the atrium and ventricle (e.g. the bundle of Kent) or within the AV node itself (see figure below).
- In re-entrant rhythms, electrical impulse can cycle and recycle repetitively.
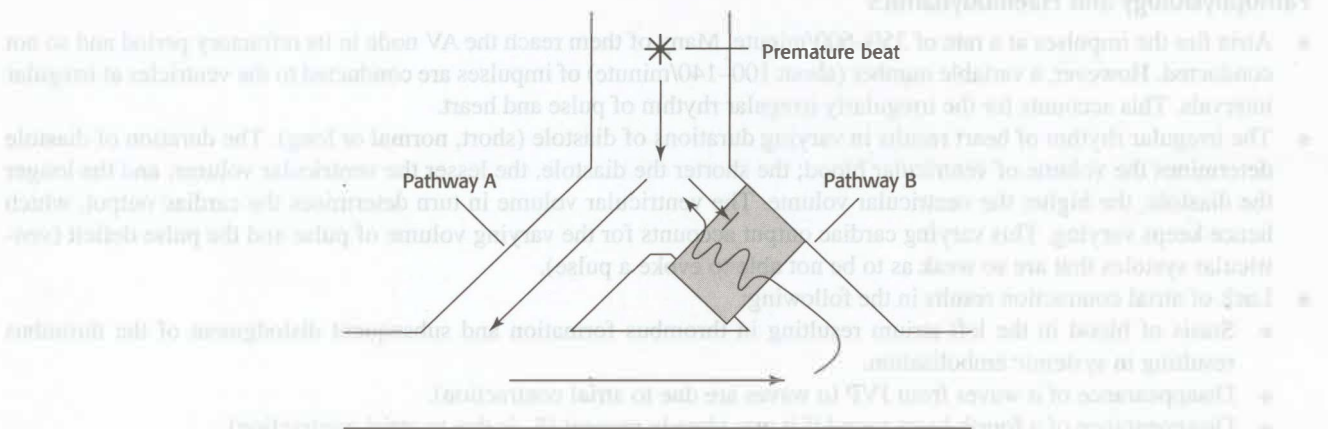
In re-entry, electrical signals generated from an appropriately timed premature beat find pathway B still under absolute refractory period, resulting in conduction block in this limb of the circuit. Meanwhile, conduction down pathway A proceeds unimpeded. Subsequent recovery of pathway B allows electrical signals to be conducted backward (or retrograde), resulting in re-activation of pathway A and propagation of the re-entry circuit.

Q. Describe sinus tachycardia.

- It is characterised by a rate more than 100/minute and normal P waves, P–R interval and QRS complexes.
- If rate-dependent blocks appear or an accessory path is present, widened QRS complexes may occur.

- It is usually seen in patients with anaemia, thyrotoxicosis, embolism, congestive heart failure and shock.
- Treatment
  - Identify underlying cause and correct it.
  - Use β-blockers if the fast rate produces myocardial ischaemia.

Q. Discuss the aetiology, pathophysiology, clinical features, complications and management of atrial fibrillation.

Definition

- This is an arrhythmia where atria are disorganised and multiple atrial foci fire impulses at a rate of 350–600/minute. There is no atrial contraction but only fibrillation. The ventricles respond at irregular intervals, usually at a rate of 100–140/minute.
- Atrial fibrillation can be paroxysmal, persistent or permanent.
  - Paroxysmal atrial fibrillation means that episodes terminate without intervention in fewer than 7 days.
  - Persistent atrial fibrillation means that episodes last longer than 7 days or require an intervention, such as cardioversion, to restore sinus rhythm.
  - Permanent atrial fibrillation means that the arrhythmia is continuous and interventions to restore sinus rhythm have either failed or not been attempted.

Aetiology

- Rheumatic heart disease (especially mitral valvular disease)
- Ischaemic heart disease (especially acute myocardial infarction)
- Hypertension
- Thyrotoxicosis
- Congenital heart diseases (especially atrial septal defect)
- Cardiomyopathy
- Pericardial diseases
- Other rare causes—alcohol, pulmonary embolism, exercise, sinoatrial disease, chronic lung diseases, electrocution.
- The term "lone atrial fibrillation" describes atrial fibrillation in elderly patients without underlying heart disease. However, at present, it is not used. Instead, the term "non-valvular atrial fibrillation" is used when it occurs in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.

Pathophysiology and Haemodynamics

- Atria fire the impulses at a rate of 350–600/minute. Many of them reach the AV node in its refractory period and so not conducted. However, a variable number (about 100–140/minute) of impulses are conducted to the ventricles at irregular intervals. This accounts for the irregularly irregular rhythm of pulse and heart.
- The irregular rhythm of heart results in varying durations of diastole (short, normal or long). The duration of diastole determines the volume of ventricular blood; the shorter the diastole, the lesser the ventricular volume, and the longer the diastole, the higher the ventricular volume. The ventricular volume in turn determines the cardiac output, which hence keeps varying. This varying cardiac output accounts for the varying volume of pulse and the pulse deficit (ventricular systoles that are so weak as to be not able to evoke a pulse).
- Lack of atrial contraction results in the following:
  - Stasis of blood in the left atrium resulting in thrombus formation and subsequent dislodgment of the thrombus resulting in systemic embolisation.
  - Disappearance of a waves from JVP (a waves are due to atrial contraction).
  - Disappearance of a fourth heart sound if it was already present (S_4 is due to atrial contraction).
  - In some cases, disappearance of pre-systolic accentuation of mid-diastolic murmur of mitral stenosis (atrial contraction may contribute to PSA).
  - Loss of "atrial booster effect" (atrial contraction in pre-systole) resulting in precipitation or worsening of cardiac failure.
- Tachycardia-related cardiomyopathy in patients with poor rate control may further depress cardiac function.

Risk of Stroke in Atrial Fibrillation

- In patients with non-valvular atrial fibrillation the average annual risk for arterial thromboembolism, including stroke, is 5%, and the risk is higher in patients older than 75 years of age.

- A risk index (CHA$_2$DS$_2$-VASc) has been developed to determine the risk of stroke due to thromboembolism in patients with non-valvular atrial fibrillation.

Risk factor	Score
Congestive heart failure	1
Hypertension	1
Age ≥75 years	2
Diabetes mellitus	1
Stroke history	2
Vascular disease (prior MI, peripheral artery disease)	1
Age 65–74 years	1
Sex category (female)	1

- CHA$_2$DS$_2$-VASc score of 9 predicts a stroke rate of 15.2% per year.
- Antithrombotic agents like warfarin are recommended for CHA$_2$DS$_2$-VASc score ≥ 2.
- In addition, echocardiographic demonstration of intra-auricular thrombus or an enlarged left atrium also indicates increased risk of emboli.

Symptoms

- Usual symptoms include palpitations, fatigue, syncope, angina and symptoms of cardiac failure and thromboembolism.

Signs

- Cardinal signs of atrial fibrillation are the following:

• Irregularly irregular pulse	• Absence of a waves on JVP
• Varying volumes of pulse	• Disappearance of the PSA of the mid-diastolic murmur of mitral stenosis (MS) in some cases
• Pulse deficit (apex-pulse deficit)	
• Varying intensity of the first heart sound	• Disappearance of the fourth heart sound
	• Hypotension

Electrocardiogram

- An irregularly irregular rhythm of QRS complexes
- Absent P waves
- Small, irregular waves (fibrillary waves) at a rate of 350–600/minute that are difficult to see on ECG (fine atrial fibrillation)
- At lower rates of 150–300, coarse fibrillary waves are seen (coarse atrial fibrillation)

Note: Patients with atrial fibrillation and digoxin toxicity may have regular R–R intervals due to development of AV block and junctional rhythm; P waves are absent.

Differential Diagnosis

- Atrial flutter with variable block: Prominent saw-tooth waves at lower rates of 250–350/minute are seen in the ECG.
- Atrial tachycardia with variable block: Atrial rate is approximately 150/minute that is regular but the conduction to the ventricles is not regular producing irregular pulse.
- Multifocal atrial tachycardia and wandering atrial pacemaker can both have irregular ventricular responses; P waves of differing morphology are present.

Complications

• Syncope	• Angina
• Thromboembolism	• Hypotension
• Precipitation/worsening of cardiac failure	• Precipitation of pulmonary oedema in mitral stenosis

Treatment

Goals of Management

- Haemodynamic stabilisation
- Control of ventricular rate

- Restoration of sinus rhythm
- Prevention of embolic complications
- Treatment of underlying cause

1. If the patient's clinical status is severely compromised (presence of hypotension, angina, syncope, pulmonary oedema or altered sensorium), synchronised DC cardioversion starting at 100 J (or 50 J using biphasic cardioverters) is the treatment of choice.
2. If the patient's clinical status is not severely compromised, treatment is in two steps:
   - Slowing the ventricular rate with verapamil, diltiazem, propranolol, esmolol or digoxin. The goal is to achieve a ventricular rate of less than 100/minute. Controlling the ventricular rate increases cardiac output, decreases the metabolic demand of the heart and avoids the potentially dangerous side effects of rhythm-control drugs. The doses of various drugs are:
     - Diltiazem: 10 mg intravenously over 2 minutes; repeat same dose in 15 minutes if required; start an infusion at 10–15 mg/hour to maintain ventricular rate below 100/minute.
     - Verapamil: 5–10 mg intravenously over 2 minutes; repeat in 30 minutes if required.
     - Propranolol: 1 mg intravenously over 2 minutes; repeat every 5 minutes up to a maximum of 5 mg.
     - Digoxin: 0.25–0.5 mg intravenously, then 0.25 mg after 4–6 hours and another dose after another 12 hours. Peak effect not seen for hours and, therefore, less commonly used at present.
     - Amiodarone: 150 mg over 10 minutes, followed by 1 mg/minute over 6 hours and then 0.5 mg/minute for next 18 hours. Drug of choice in stable patients with known ejection fractions of less than 40%. Less likely to produce fall in blood pressure compared to other drugs. However, it may convert atrial fibrillation to normal rhythm that may lead to embolism. Adverse effects of amiodarone include the following:
       - Hepatic toxicity characterised by hepatitis that can progress to cirrhosis.
       - Pulmonary toxicity can develop within 6 weeks or after years of therapy and most often manifests as cough and dyspnoea
       - Thyroid dysfunction (hypothyroidism, hyperthyroidism)
       - Sun sensitivity
       - Ocular symptoms
   - Converting rhythm to normal sinus rhythm
     - Pharmacological cardioversion to sinus rhythm with quinidine, ibutilide, flecainide, propafenone or amiodarone. The dose of amiodarone 5–7 mg/kg intravenously over 1 hour followed by 1.2–1.8 g/24-hour infusion.
     - If medical cardioversion fails, electric cardioversion is performed after 3 weeks of warfarin therapy that is continued for another 4 weeks after cardioversion.
     - Anticoagulation is recommended in such patients (see below).
3. If sinus rhythm is restored by electric or pharmacological cardioversion, amiodarone, dronedarone, flecainide, propafenone or sotalol may be used to prevent recurrence. Dronedarone, though has betters safety profile compared to amiodarone, should not be used to control rate in patients with permanent atrial fibrillation or those with heart failure as it increases risk of stroke, MI and death.
4. In patients in whom cardioversion is unsuccessful or in whom atrial fibrillation is likely to recur, treatment consists of the following:
   - Allowing the patient to remain in atrial fibrillation but reduce the ventricular rate by digitalis, diltiazem, verapamil or propranolol. Goal is to achieve a resting heart rate of 80/minute.
   - Chronic anticoagulation
5. Antithrombotic therapy:
   - Early medical or electric cardioversion may be done without prior anticoagulation therapy when atrial fibrillation has been present for less than 48 hours.
   - If duration of atrial fibrillation exceeds 48 hours or is unknown, a transoesophageal echocardiography should be done to exclude an atrial thrombus. If no atrial thrombi are observed heparin is administered before cardioversion (if conversion to sinus rhythm is planned) that is followed by warfarin for 4 weeks.
   - If atrial thrombi are seen on echocardiography, cardioversion should be delayed and anticoagulation with warfarin is administered for 3 weeks prior to cardioversion. Warfarin is continued for another 4 weeks after cardioversion.
   - If cardioversion is unsuccessful and patient remains in atrial fibrillation, or cardioversion is not planned, long-term warfarin therapy is recommended if CHA_2DS_2-VASc score ≥ 2, or patient has a previous history of stroke or transient ischaemic attack.

- Thus, anticoagulants are required in all three types of atrial fibrillation i.e. paroxysmal, persistent and permanent.
- Anticoagulants include warfarin, dabigatran (a direct thrombin inhibitor) or apixaban (a direct factor Xa inhibitor).
- With warfarin, the INR should be maintained between 2.0 and 3.0 (between 2.5 and 3.5 if underlying valvular lesion is present).

6. Aspirin:
   - Aspirin 325 mg/day can be used as an alternative to warfarin in the following situations:
     - Contraindication/allergy to warfarin; or
     - Age <75 years with no previous stroke or transient ischaemic attack; and no hypertension, diabetes or heart failure.

7. Refractory cases are managed with antitachycardia pacemakers or inducing complete heart block by ablation of bundle of His followed by permanent pacemaker implantation.

Note: Rate-control strategies advocate medically slowing ventricular response to the fibrillating atrium and using anticoagulation to reduce stroke risk. On the other hand, rhythm-control strategies involve medical or electrical conversion to sinus rhythm to improve haemodynamics and symptoms and, theoretically, reduce stroke risk. However, data available suggest no definite advantage of one approach over the other. Rate control along with chronic anticoagulation is possibly the best strategy for most patients with atrial fibrillation. In some select group patients (e.g. young patients or patients with left ventricular dysfunction producing symptoms) rhythm control may be tried, even though there is no data to support this line of action.

Q. Define atrial flutter. Discuss the causes, electrocardiographic features and management of atrial flutter.

- Definition
  - Atrial flutter is characterised by a regular, rapid atrial rate of 250–350/minute, where ventricles respond to every second, third or fourth beat (2:1, 3:1 or 4:1 AV block).
- Common causes
  - Organic heart diseases (ischaemic, rheumatic, congenital)
  - Pericarditis
  - Acute respiratory failure
  - First week following open heart surgery
- Electrocardiographic feature
  - Characteristic flutter waves are seen as regular saw-toothed waves ("F" waves).
- Management
  - Immediate conversion to sinus rhythm can be accomplished by direct current cardioversion or atrial pacing.
  - Initial reduction of ventricular rate using digoxin, diltiazem, β-blockers or verapamil followed by conversion to sinus rhythm using quinidine, amiodarone, disopyramide or flecainide.
  - Prevention of recurrences can be accomplished by quinidine, amiodarone, disopyramide or flecainide.
  - The stroke risk is similar to that for atrial fibrillation and the management of anticoagulation is almost identical but may be stopped earlier after successful ablation.

Q. Write a short note on paroxysmal supraventricular tachycardia (PSVT).

- It is usually paroxysmal and recurrent, and has a rate of 140–220 beats/minute with 1:1 conduction.
- It usually results from re-entry of an atrial ectopic in the AV node (AV nodal re-entry tachycardia—AVNRT). PSVT can also result from re-entry in the accessory pathways [AV re-entry tachycardia (AVRT)]. Occasionally, it results from increased atrial automaticity.
- Usually, AVRT is orthodromic with activation transmitted from atria to ventricles via the AV node and back via the accessory pathway ("orthodromic" because the AV node is conducting in the "correct direction"). Less commonly, the direction of activation is antidromic that leads to aberrant ventricular activation and broad QRS complexes.
- It is often difficult to differentiate AVNRT and AVRT on the basis of ECG.
- Causes
  - Idiopathic in healthy individuals
  - Excessive coffee, tea, alcohol or tobacco
  - Anxiety

- Hyperthyroidism
- Organic heart disease (ischaemic, valvular or congenital)
- Clinical features
  - The onset and termination of the arrhythmia are sudden.
  - Patients most commonly complain of palpitations, an odd feeling in the chest and on occasion, lightheadedness or syncope.
  - Those with significant heart disease may have additional symptoms during the arrhythmia such as dyspnoea and chest pain.
  - Some patients have polyuria and experience diuresis during or after PSVT.
  - Electrocardiogram
  - The P wave is usually buried in the QRS complex or occurs slightly before or after the QRS complex.
  - The QRS complexes occur at regular intervals (there is constant RR cycle length) and are similar to those seen during sinus rhythm since activation of the ventricular myocardium is unaltered and is via the His–Purkinje system.
  - Significant ST segment depression during tachycardia has been observed in 25–50% of patients. Majority of these patients do not have underlying coronary artery disease.
- Treatment
  - Vagal manoeuvres like carotid sinus massage, Valsalva manoeuvre and gag reflex are useful. These manoeuvres delay conduction in AV node in a patient with circuit tachycardia.
  - If vagal manoeuvres are unsuccessful, drug therapy is warranted. These drugs include propranolol, esmolol, verapamil, diltiazem and adenosine. They prolong the AV refractory period.
  - Adenosine is administered as an initial bolus of 6 mg rapidly over 1–3 seconds followed immediately by 20 mL of saline. If required, a second and third dose of 12 mg is repeated in 1–2 minutes.
  - Synchronised cardioversion is performed if patient is haemodynamically compromised.
  - Long-term control can be achieved by radiofrequency ablation of the re-entrant pathway.

Q. Discuss briefly Wolff–Parkinson–White syndrome (WPW syndrome).

- Cause—Presence of an abnormal band of atrial tissue connecting the atria and ventricles and bypassing the AV node.
- During sinus rhythm conduction takes place partly through the AV node and partly through the bypass tract. This results in a short PR interval (<0.12 seconds), a delta wave in the beginning of QRS complex due to activation of ventricles via the accessory pathway, and prolonged QRS complex (>0.12 seconds) due to fusion of excitation via two pathways.
- This tract can act as a re-entry pathway and the patient may develop supraventricular tachycardia.
- Complications
  - Supraventricular tachycardia, atrial fibrillation, ventricular tachycardia, ventricular fibrillation (VF) and death.
- Treatment
  - Narrow complex tachycardia is treated in the same way as PSVT.
  - For broad-complex tachycardia, isopyramide, quinidine, flecainide, propafenone and amiodarone are useful as these drugs increase the refractory period and reduce the conduction rate through the bypass tract.
  - In selected cases radiofrequency ablation of the bypass tract can be done.
  - In patients with WPW syndrome and atrial fibrillation, cardioversion is the treatment of choice. Caution should be employed when using digitalis, adenosine or verapamil in patients of WPW syndrome and atrial fibrillation because increase in AV nodal refractory period produces increased conduction through the accessory pathway which may precipitate ventricular fibrillation.

Q. Explain briefly about sick-sinus syndrome.

- The term "sick-sinus syndrome" encompasses a number of abnormalities including sinus bradycardia, sinus arrest, combinations of sinoatrial and AV blocks, and supraventricular tachycardias, particularly atrial fibrillation and flutter.
- Defined by abnormal cardiac impulse formation and by abnormal propagation from the sinoatrial node which prevent it from performing its pacemaking function. It is characterised by sinus node dysfunction with an atrial rate inappropriate for physiologic requirements.

- The abnormalities are usually due to ischaemia, fibrosis (often age-related and produced by dysfunction of ion channels within SA), drug-induced (beta blockers, calcium channel blockers, digoxin, sympatholytic medications, antiarrhythmic medications, lithium), infiltrative disorders (haemochromatosis, sarcoidosis, connective tissue diseases) or autonomic dysfunction.
- Clinical features:
  - Many patients are asymptomatic.
  - In others, clinical features are related to cerebral hypoperfusion and reduced cardiac output. These can include syncope, palpitations and dizziness as well as symptoms caused by worsening of underlying conditions such as congestive heart failure, angina pectoris and cerebrovascular accident.
  - Peripheral thromboembolism and stroke, which can occur in the presence of bradycardia–tachycardia syndrome (alternating bradyarrhythmias and tachyarrhythmias), may be related to dysrhythmia-induced emboli.
  - A slow heart rate in the presence of fever, left ventricular failure or pulmonary oedema may be suggestive of sick-sinus syndrome.
- Treatment of recurrent symptomatic bradycardia or prolonged pauses requires implantation of a permanent pacemaker.

Q. Explain briefly about ventricular tachycardia.

- It is a wide complex tachycardia (rate >100/minute) with regular rate and single QRS morphology. Non-sustained ventricular tachycardia (VT) is a series of repetitive ventricular beats that have a duration of less than 30 seconds; sustained VT lasts for more than 30 seconds.
- Causes
  - It usually occurs in the presence of some underlying heart disease and is rarely seen in normal hearts.
- Clinical features
  - The patient may be asymptomatic or may present with palpitations or haemodynamic collapse.
  - The assumption that a haemodynamically stable patient cannot have VT is erroneous.
- Electrocardiogram
  - The width of the QRS complex is generally >0.16 second.
  - Positive or negative concordance of the QRS complex across the pre-cordial leads (e.g. R waves or S waves only).
  - A monophasic "Rr" pattern in lead V_1 (termed rabbit ears) with a taller left ear.
  - An indeterminate axis (between –90° and –180°).
  - In severe underlying heart disease the QRS morphology may be variable (polymorphic VT). The basal QT interval before onset of polymorphic VT is normal as compared to torsades de pointes.
- Treatment
  - If the patient is haemodynamically unstable in the form of hypotension, angina, heart failure or altered sensorium, immediate cardioversion in synchronised mode is required.
  - If the patient is stable, amiodarone and lidocaine are the drugs of choice.
    - Amiodarone 150 mg intravenously over 10 minutes, then 1 mg/minute for 6 hours and then 0.5 mg/minute for next 18 hours.
    - Lidocaine 1–1.5 mg/kg IV over 1 minute followed by infusion at 10–40 µg/kg/minute. A repeat bolus of 50 mg may be required during the first 30 minutes to avoid subtherapeutic blood levels.

Q. Write a short note on Torsades de pointes.

- It is a special type of VT characterised by gradual changing of QRS axis so that it appears to twist around the isoelectric line.
- Causes
  - The baseline ECG shows prolonged Q–T interval.
  - It can result from ingestion of certain drugs like quinidine, procainamide, antidepressants and phenothiazines, and electrolyte imbalances like hypokalaemia and hypocalcaemia.
- Most of the episodes of torsades are self-limiting and do not produce haemodynamic compromise. However, these attacks may precipitate VF.
- Treatment
  - Recurrence rates of torsades after spontaneous resolution are quite high. Therefore, treatment is primarily directed to prevent the recurrences rather than to terminate a given episode.
  - Magnesium in a dose of 2–4 g IV over a period of 30 minutes is quite effective in terminating an episode and preventing its recurrence.

- Because the occurrence of torsades de pointes is dependent upon relative bradycardia, isoproterenol and overdrive pacing are also usually effective.

Q. Give a brief outline of Brugada syndrome.

- It is characterised by ST segment elevation (≥ 2 mm) in right pre-cordial leads (V_1 to V_3) followed by inverted T waves, incomplete or complete right bundle branch block, and susceptibility to ventricular tachyarrhythmia (particularly polymorphic ventricular tachycardia) and sudden cardiac death.
- Syncope due to tachyarrhythmia usually occurs during sleep or at rest.
- Typically presents in third or fourth decade.
- Similar ECG patterns are seen in anterior wall infarction, arrhythmogenic right ventricular dysplasia, acute pericarditis, Duchenne muscular dystrophy, hypercalcaemia and hyperkalaemia.
- Genetically transmitted as an autosomal dominant syndrome with incomplete penetrance.
- Treatment involves implantable cardioverter defibrillator (ICD) in patients who have experienced at least one attack of cardiac arrest. Quinidine may be used if ICD implantation is not feasible. It can also be used along with ICD to reduce number of shocks delivered by ICD.

Q. What is commotio cordis?

- Commotio cordis is occurrence of VF and sudden death triggered by a blunt, non-penetrating and often innocent-appearing unintentional blow to the chest without damage to the ribs, sternum or heart (and in the absence of underlying cardiovascular disease).
- In Latin, it means agitation of the heart.
- Occurs primarily in children, adolescents and young adults.
- Occurs immediately following inciting factor.

Q. Write a short note on sudden cardiac death (SCD).

- Sudden cardiac death (SCD) is defined as an unexpected, non-traumatic death due to cardiac causes occurring in a short time period (generally within 1 hour of symptom onset) in a person with known or unknown cardiac disease in whom no previously diagnosed fatal condition is apparent.
- Nearly 85% of SCDs occur due to ventricular arrhythmias (either primary VF or brief ventricular tachycardia degenerating to VF).

Causes

• Coronary artery disease	• Congenital heart disease
• Ischaemic cardiomyopathy	• Long QT syndrome
• Non-ischaemic cardiomyopathy	• Brugada syndrome
• Hypertrophic cardiomyopathy	• Wolff–Parkinson–White syndrome
• Aortic dissection	• Early repolarisation syndrome
• Arrhythmogenic right ventricular dysplasia	• Electrolyte abnormalities
• Arrhythmia from antiarrhythmic agents	• Sarcoidosis
• Cocaine	• Amyloidosis
• Myocarditis	• Cardiac tumours
• Valvular heart disease (e.g. aortic stenosis)	

Treatment

- It involves primary prevention (preventing SCD in patients with high-risk conditions), secondary prevention (preventing SCD in patients revived from SCD) and cardiopulmonary resuscitation (CPR) in patients presenting cardiac arrest.
  - Traditional antiarrhythmic agents have either been ineffective in preventing/reducing sudden death or have increased sudden death and therefore are not recommended.
  - β-blockers, ACE inhibitors and spironolactone may be of some benefit.
- ICD is the primary treatment modality in most patients.

- Radiofrequency ablation for patients with AV bypass tracts, bundle-branch block-associated VT, arrhythmogenic right ventricular dysplasia—conditions uncommonly seen.

Q. Define cardiac arrest. What are the causes of cardiac arrest? How do you manage it?

Q. Explain about cardiopulmonary resuscitation (CPR).

Definition

- Cardiac arrest is defined as an abrupt loss of cardiac pump function which may be reversible by a prompt intervention, but will lead to death in its absence.
- Cardiac arrest may result from one of the following four mechanisms: 1. VF. 2. Pulseless ventricular tachycardia. 3. Asystole. 4. Pulseless electrical activity (PEA).

Causes

Ventricular fibrillation	Ventricular asystole
- Myocardial ischaemia or infarction	- Localised failure of conducting tissue
- Electrocution	- Massive myocardial infarction
- Other structural heart diseases	**Pulseless electrical activity (PEA)**
- Hypokalaemia and hyperkalaemia	- Cardiac rupture
- Drugs	- Massive pulmonary embolism

Note

1. Initial rhythm of VT may degerate into PEA or asystole with passage of time
2. Reversible causes of refractory VT/VF, asystole and PEA are 6 Hs and 6Ts, and have been listed later.

Management [Cardiopulmonary Resuscitation (CPR)]

- Cardiopulmonary resuscitation provides artificial ventilation and perfusion to the vital organs, particularly heart and brain until spontaneous cardiopulmonary function is restored.
- It encompasses both basic life support (BLS) and advanced life support (ALS).
- Successful resuscitation following cardiac arrest requires an integrated set of coordinated actions represented by the links in the "Chain of Survival".

Links in the Chain of Survival

- Immediate recognition of cardiac arrest and activation of the emergency response system (ERS)
- Early CPR with an emphasis on chest compressions
- Rapid defibrillation
- Effective advanced life support (ALS)
- Integrated post-cardiac arrest care

Basic Life Support

- Basic life support (BLS) indicates manoeuvres which, without special equipment (except automated external defibrillator and a protective shield), either prevent circulatory and respiratory arrest or externally support the circulation and ventilation of a victim in arrest.
- The major goal of BLS is to provide adequate oxygen and perfusion to vital organs (brain and heart) until advanced cardiac life support is available.
- Most out-of-hospital cardiac arrests occur following a myocardial injury and present initially with VF or pulseless VT. The patient is therefore likely to be responsive to defibrillation that has become a part of BLS.
- Immediate recognition and activation of ERS, early CPR and rapid defibrillation (when appropriate) are the first three BLS links in the adult Chain of Survival.

Immediate Recognition and Activation of Emergency Response System (ERS)

- Early recognition that a cardiac arrest has occurred is the key to survival. For every minute a patient is in cardiac arrest the chances of survival drop by roughly 10%. If a patient is unresponsive, he/she is presumed to be in cardiac arrest.
- If a lone rescuer finds an unresponsive adult (i.e. no movement or response to stimulation) or witnesses an adult who suddenly collapses, he/she should first ensure that the scene is safe.
- Rescuer should then check for a response by tapping the victim on the shoulder and shouting at the victim.
- If the victim also has absent or abnormal breathing (i.e. only gasping), the rescuer should assume the victim is in cardiac arrest. The trained or untrained lay person should activate the ERS.
  - If other rescuers are present, the first rescuer should direct them to activate the ERS and get the automated external defibrillator (AED); the first rescuer should start CPR immediately.
  - If the rescuer is not trained in recognising abnormal breathing, the lay rescuer should phone the ERS once the rescuer finds that the victim is unresponsive; the dispatcher at ERS should be able to guide the lay rescuer to check for breathing and the steps of CPR.
  - The health-care provider can check for response and look for no breathing or no normal breathing (i.e. only gasping) before activating the ERS.
- After activation of the ERS, all rescuers should immediately begin CPR for adult victims who are unresponsive with no breathing or no normal breathing (only gasping). The rescuer should treat the victim who has occasional gasps as if he or she is not breathing.
- A health-care provider can tailor the sequence of rescue actions to the most likely cause of arrest. For example, if a lone health-care provider sees an adolescent suddenly collapse, the provider may assume that the victim has suffered a sudden cardiac arrest; he/she activates ERS immediately to get an AED, and then returns to the victim to provide CPR. If a lone health-care provider finds an adult drowning victim or a victim of foreign body airway obstruction who becomes unconscious, the health-care provider may give about 5 cycles (approximately 2 minutes) of CPR before activating ERS.

Pulse Check

- Both lay rescuers and health-care providers have difficulty detecting a pulse. Further, health-care providers also may take too long to check for a pulse.
  - Therefore, lay rescuer should not check for a pulse and should assume that cardiac arrest is present if an adult suddenly collapses or an unresponsive victim is not breathing normally.
  - The health-care provider may palpate pulse (carotid artery) but should take no more than 10 seconds to check for a pulse and, if the rescuer does not definitely feel a pulse within that time period the rescuer should start chest compressions.

Early Cardiopulmonary Resuscitation (CPR)

- CPR includes four sequential steps: Circulation, Airway and Breathing (CAB) and defibrillation. Previously, the sequence used to be Airway, Breathing and Circulation (ABC).

Circulation

- Circulation is achieved by chest compressions.
- Chest compressions consist of forceful rhythmic applications of pressure over the lower-half of the sternum. These compressions create blood flow by increasing intrathoracic pressure and directly compressing the heart. This generates blood flow and oxygen delivery to the myocardium and brain.
- Effective chest compressions are essential for providing blood flow during CPR. For this reason all patients in cardiac arrest should receive chest compressions.
- For cardiac compression the patient should be in a supine position on a firm surface.
- The rescuer should place the heel of one hand on the centre (middle) of the victim's chest (i.e. lower-half of the sternum) and the heel of other hand on top of the first so that the hands are overlapped and parallel to each other.
- Chest compression is performed at a rate of 100/minute with the compression phase occupying at least 50% of the whole cycle of compression–relaxation ("duty cycle"). The compression depth should be at least 2 inches (5 cm). Rescuers should allow complete recoil of the chest after each compression to allow the heart to fill completely before the next compression.
- The rate of compression refers to the speed of compressions, not the actual number of compressions delivered per minute. The actual number of chest compressions delivered per minute is determined by the rate of chest compressions and the number and duration of interruptions (e.g. to open the airway, deliver rescue breaths and allow AED analysis).
- The rescuer should "push hard, push fast", and allow the chest to recoil after each compression.

- In both single-rescuer and two-rescuers CPR, 30 compressions are delivered followed by 2 breaths. However, only "hands-on" CPR is also recommended for lay person who is reluctant to give mouth-to-mouth respiration or is not trained in that.
- The rescuer should interrupt chest compression as infrequently as possible and should limit interruptions to no more than 10 seconds at a time.
- When more than one rescuer is present, rescuers should change roles after every 2 minutes or five cycles of CPR. Consider switching rescuers during any intervention associated with appropriate interruptions in chest compressions (e.g. when an AED is delivering a shock). Every effort should be made to accomplish this switch in <5 seconds.
- Pre-cordial thump: There is only anecdotal evidence that the electric current produced by pre-cordial thump may terminate VF. On the other hand, there is evidence that one thump may convert VT into VF or asystole. Therefore, a thump should not be attempted in unwitnessed cardiac arrests.

Airway

- The trained lay rescuer who feels confident that he/she can perform both compressions and ventilations should open the airway using a head tilt-chin lift manoeuvre.
- A health-care provider should use the head tilt-chin lift manoeuvre to open airway of a victim with no evidence of head or neck trauma.
- For victims with suspected spinal injury, rescuers should initially use manual spinal motion restriction (e.g. placing one hand on either side of victim's head to hold it still) while performing compressions. If health-care providers suspect a cervical spine injury, they should open the airway using jaw thrust method. However, if he/she fails to open the airway using jaw thrust, head tilt-chin lift manoeuvre should be done.
  - In head tilt-chin lift method the chin is moved forward with the index and middle fingers of one hand while the other hand is placed over the forehead so as to flex the neck in relation to the chest and extend the head in relation to the neck.
  - In jaw-thrust method the angles of mandible are grasped with both hands and the mandible is lifted forward.

Breathing

- After opening the airway, mouth-to-mouth or mouth-to-nose or mouth-to-mask or bag-mask breathing is started with compression: ventilation ratio of 30:2 (i.e. at a rate of 8–10/minute).
  - To provide mouth-to-mouth rescue breaths, open the victim's airway, pinch the victim's nose and create an airtight mouth-to-mouth seal. Give one breath over one second, taking normal (and not deep) breath. Each rescue breath is delivered over 1 second. If the victim's chest does not rise with the first rescue breath, reposition the head by performing the head tilt-chin lift again and then give the second rescue breath. Volume of each rescue breath should produce visible chest rise.
  - Bag-mask ventilation is not the recommended method of ventilation for a lone rescuer during CPR. It is most effective when provided by two trained and experienced rescuers. One rescuer opens the airway and seals the mask to the face while the other squeezes the bag.
- When an advanced airway (i.e. endotracheal tube, Combitube or laryngeal mask airway) is in place during CPR, give 1 breath every 6 to 8 seconds without attempting to synchronise breaths between compressions; this will result in delivery of 8 to 10 breaths/minute. There should be no pause in chest compressions for delivery of ventilations after advanced airway in place. Tidal volume per breath should be 6–7 mL/kg (about 600 mL in adults). Excessive ventilation is unnecessary and can cause gastric inflation and its resultant complications, such as regurgitation and aspiration. More important, excessive ventilation can be harmful because it increases intrathoracic pressure, decreases venous return to the heart and diminishes cardiac output and survival.

Early Defibrillation

- The importance of early cardiac defibrillation in patients of cardiac arrest has led to the development of AEDs. Since VF and pulseless VT are the major causes of cardiac arrest in adults, application of early defibrillation in field setting by the paramedics is important.
- Defibrillator should be used as soon as it is available and is not to be used only after CAB have been completed.
- AEDs are capable of analysing cardiac rhythm and if appropriate, advise/deliver an electric countershock. The operator merely places two self-adhesive electrode pads onto the patients and administers a shock when advised, standing clear when the AED is ready to discharge.
- If a shockable rhythm is detected, one shock at 360 J (monophasic defibrillators) or 150–200 J (biphasic defibrillators) is given.
- CPR should be started immediately following one shock and continued for five cycles of 30:2 compression-to-ventilation ratio before re-checking the rhythm.

Advanced Life Support

- Advanced life support (ALS) consists of BLS (CAB and early defibrillation) followed by use of special equipment and drugs for establishing and maintaining effective ventilation and circulation (ABCD) where *D* stands for defibrillation and for differential diagnoses which include treatable causes of cardiac arrest.

Advanced Airway

- It includes the use of oral and nasal airways, bag mask, orotracheal and nasotracheal endotracheal tubes for intubations, oesophageal–tracheal combitube, laryngeal mask airway, and surgical procedures like cricothyrotomy and tracheostomy.

Advanced Breathing

- Confirmation of endotracheal tube placement using both clinical assessment (tube seen passing through vocal cords; five-point auscultation—over epigastrium, left and right anterior chest, and left and right mid-axillary parts of chest; condensation of water vapour inside the tube) and use of a device (e.g. exhaled carbon dioxide detector or end-tidal CO_2 capnograph, oesophageal detector device). End-tidal carbon dioxide is the gold standard to confirm position of tube in trachea.
- Securing the endotracheal tube using tube holders (which are better than using tape or bandage to hold the tube).
- Ventilate at a tidal volume of 6–7 mL/kg and at a rate of 8–10 breaths/minute.
- Confirm effective ventilation and oxygenation by end-tidal CO_2 monitor and oxygen saturation monitor.

High Quality CPR

- Push hard (≥2 inches or 5 cm) and fast (≥100/minute)
- Allow chest wall to recoil back completely in between two compressions
- Minimise interruptions during chest compressions
- Rotate chest compressor every 2 minutes
- Avoid excessive ventilation
- 30:2 chest compression:ventilation ratio if advanced airway not in place
- If end tidal CO2 <10 mmHg by quantitative waveform capnography, improve CPR quality
- If intra-arterial relaxation phase pressure <20 mmHg, improve CPR quality

Advanced Circulation

- It includes continuation of chest compression along with establishing an intravenous access, attaching a cardiac monitor/defibrillator and assessing the rhythm, defibrillation and administering drugs appropriate for rhythm and condition.
- With advanced airway in place, rescuers no longer provide cycles of compression with pauses for ventilation. The compression is done continuously at the rate of 100/minute and ventilation is provided at 8–10 breaths/minute (1 breath every 6–8 seconds).
- Basic rhythms commonly seen in patients with cardiac arrest include ventricular fibrillation (VF), pulseless VT, asystole and PEA. Of these, VT and fibrillation are the most common rhythm and are most amenable to therapy.
- Rhythm checks should be done only after 2 minutes of CPR and not immediately following a defibrillation attempt.
- Pulse check should be performed only after 2 minutes of CPR if the monitor shows a change in rhythm from previous one or it shows an organised rhythm.

Ventricular Fibrillation or Pulseless Ventricular Tachycardia (VT) (Shockable Rhythms)

- As soon as a defibrillator is available, it should be used for early conversion of the fibrillating heart to normally contracting heart. One shock at 360 J (monophasic defibrillators) or 150–200 J (biphasic defibrillators) is given that is followed by CPR immediately without checking the rhythm or the pulse.
- Continue CPR for 2 minutes, then pause briefly to check the monitor for rhythm. If VT/VF persists:
  - Give second shock of same energy, resume CPR immediately and continue for 2 minutes, and repeat this cycle.
  - Immediately following second shock give adrenaline (epinephrine) intravenously in a dose of 1 mg (1 mL of 1:1000 solution) as an IV bolus followed by a rapid bolus of 20 mL of saline and elevating the arm up. If IV access is not available, intraosseous (IO) route should be accessed.

- If VT/VF persists, continue giving shock every 2 minutes.
- Repeat adrenaline every 3–5 minutes if VT/VF persists.
- One dose of vasopressin, 40 U, may replace either the first or the second dose of adrenaline.
- If after two doses of adrenaline VT/VF persists, administer amiodarone 300 mg IV followed by 150 mg after 3–5 minutes if VT/VF persists; start amiodarone infusion (maximum cumulative dose: 2.2. g over 24 hours).
- If amiodarone is not available or is not effective, give lidocaine. The initial dose of lidocaine is 1 to 1.5 mg/kg IV bolus. If VF or pulseless VT persists, additional doses of 0.5 to 0.75 mg/kg IV push may be administered at 5 to 10 minute intervals to a maximum dose of 3 mg/kg.
- Look for reversible causes if VT/VF persists.
- If organised electrical activity is seen during brief pause in compressions every 2 minutes, check for pulse.
  - If a pulse is present, start post-resuscitation care.
  - If a pulse is not present, continue CPR and switch to non-shockable rhythm sequence if VT or VF disappear.

Pulseless Electrical Activity (PEA) and Asystole (Non-Shockable Rhythms)

- PEA is defined as cardiac electrical activity in the absence of any palpable pulse. These patients often have some mechanical myocardial contractions but they are too weak to produce a detectable pulse. Asystole is commonly seen in patients of unwitnessed sudden cardiac arrest outside the hospital and in critically-ill patients, and is nearly always fatal. Both are non-shockable rhythms.
- If the rhythm is PEA or asystole:
  - If cardiac monitor/defibrillator monitor shows PEA or asystole, start CPR, beginning with chest compressions, and should continue for 2 minutes before the rhythm check is repeated.
  - Give adrenaline 1 mg IV as soon as feasible.
  - Re-check rhythm after 2 minutes of CPR.
  - If PEA or asystole persists, continue CPR, re-check rhythm every 2 minutes and give adrenaline every 3–5 minutes. Vasopressin can replace first or second dose of adrenaline. Atropine is no longer recommended in PEA or asystole.
  - If rhythm check shows change in rhythm, check for pulse. If pulse is present, start post-resuscitation care. If pulse is absent, continue CPR with rhythm check every 2 minutes and adrenaline every 3–5 minutes.
  - In case of asystole check that the leads are connected properly and the gain on monitor is set at maximum.
  - If at any time the rhythm develops into VF/VT, defibrillate the patient.
  - Look for reversible causes (see differential diagnoses below) that can produce PEA.
- CPR can be stopped if:
  - VF:VT eliminated.
  - Advanced airway device placed and position confirmed.
  - Proper oxygenation and ventilation ensured using oxygen saturation monitor and end-tidal CO_2 monitor.
  - All rhythm-appropriate drugs administered.
  - All potentially reversible causes excluded.
  - CPR performed for 10 minutes after the rhythm confirmed to be PEA/asystole.

Differential Diagnoses

- Try to search for reversible causes producing cardiac arrest rhythm and treat them. These causes have been listed as "6 Hs and 6 Ts".

Reversible Causes of Cardiac Arrest

Six Hs	Six Ts
- Hypoxia	- Tamponade, cardiac
- Hypovolaemia	- Tension pneumothorax
- Hypothermia	- Toxins/tablets
- Hydrogen ions (acidosis)	- Thrombosis, coronary (myocardial infarction)
- Hypokalaemia/hyperkalaemia	- Thrombosis, pulmonary embolism
- Hypoglycaemia	- Trauma

Miscellaneous Drugs in Cardiac Arrest

- Sodium bicarbonate was widely used in patients with cardiopulmonary arrest with the objective of managing acidaemia in these patients. However, no benefit has been shown when it is administered early during the CPR. In fact, bicarbonate may be detrimental to the patient. It may be used in patients with cardiac arrest related to hyperkalaemia or tricyclic antidepressant poisoning.
- Calcium had been used commonly in patients with asystole and EMD. However, because of the potential role of intracellular calcium accumulation in irreversible ischaemic cell injury, calcium is now recommended only if there is some evidence to suggest hypocalcaemia, hyperkalaemia or calcium-channel blocker overdose.
- Fibrinolytic therapy (e.g. streptokinase, tenecteplase, etc.) should not be routinely used in cardiac arrest. When pulmonary embolism is presumed or known to be the cause of cardiac arrest empirical fibrinolytic therapy can be considered.

Post-Resuscitation Care

- Ensure an adequate airway and support breathing. Hyperventilation should be avoided for routine care. Start at ventilation of 10–12/minute and ensure end-tidal CO_2 of 35–40 mmHg. Although 100% oxygen may have been used during initial resuscitation, titrate inspired oxygen to the lowest level required to achieve an arterial oxygen saturation of 94%, so as to avoid potential oxygen toxicity.
- Continuous cardiac monitoring.
- Use vasoactive medications and fluids to support circulation. Drugs include norepinephrine, dobutamine and epinephrine.
  - Epinephrine—0.1–0.5 μg/kg/minute
  - Dopamine—5–10 μg/kg/minute
  - Norepinephrine—0.1–0.5 μg/kg/minute
- Avoid hyperthermia.
- Hypothermia (32–34°C) for 12–24 hours may be considered for any patient who is unable to follow verbal commands after resuscitation from cardiac arrest. One of the techniques recommended is to infuse 1–2 litres of ice-cold isotonic saline or Ringer's lactate. Clinicians should continuously monitor the patient's core temperature using an oesophageal thermometer, bladder catheter in non-anuric patients or pulmonary artery catheter if one is placed for other indications.
- Avoid hyperglycaemia; maintain blood sugar <200 mg/dL.
- Overall the most common cause of cardiac arrest is cardiovascular disease and coronary ischaemia. Therefore, ECG should be obtained as soon as possible to detect ST elevation or new or presumably new left bundle branch block.
- Attention should be directed to treating the precipitating cause of cardiac arrest ("Hs" and "Ts").

Q. Discuss the causes, clinical features and management of atrioventricular blocks.

First Degree Block

- First degree AV block may be associated with electrolyte disturbances, use of digitalis, β-blockers or calcium channel blockers, and acute myocardial infarction (usually inferior wall).
- It is usually asymptomatic.
- In the ECG, the P–R interval is prolonged to more than 0.20 seconds. All the P waves are conducted and the QRS is normal as the delay is most often in the AV node.
- Treatment includes correction of any electrolyte imbalance and removal of an offending agent. If it occurs as a result of acute MI, the patient should be observed to detect any progression to higher degrees of blocks.

Second Degree Block

- It can be subdivided into Mobitz type I and Mobitz type II blocks.
- Mobitz type I (Wenckebach) second degree AV block.
  - It usually occurs in acute inferior wall myocardial infarction and use of digitalis, β-blockers or calcium channel blockers.
  - The block is usually transient and the patient is usually asymptomatic.
  - It is characterised by progressive slowing of AV conduction until it is totally blocked. The ECG typically shows progressive prolongation of successive P–R intervals until one P wave is not conducted. The QRS is usually normal.
  - If the patient is symptomatic, atropine should be administered. Pacing is usually not required.
- Mobitz type II second degree AV block.
  - This type of block usually occurs after anterior wall MI.
  - The patients are usually symptomatic (see complete heart block) and there are high chances of its progression to third degree AV block.
  - The block is characterised by a constant P–R interval with intermittent failure of atrial impulses to conduct to the ventricles. The block is defined by a ratio in which the first digit represents the total number of P waves and the second digit represents the number of P waves conducted, i.e. the number of QRS complexes. Thus, in a 3:1 block, of three P waves, one is conducted while two are blocked.

- It occurs most often due to delay in conduction in the His-bundle and Purkinje system and, therefore, the QRS is often abnormal.
- Patients generally require a pacemaker. Atropine is of little use while response to isoproterenol is variable.

Third Degree or Complete AV Block

- In complete heart block, none of the atrial impulses reach the ventricles. The atria are thus activated by one pacemaker, usually the sinus pacemaker. The ventricles are activated by another pacemaker situated either in the bundle of His or ventricles.

Causes of Complete Heart Block

Congenital
Acquired

- Lenegre's disease	- Digitalis intoxication
- Lev's disease	- Infective endocarditis
- Myocardial ischaemia or infarction	- Tumours and infections involving the conducting system
- Intracardiac surgery	

- Lenegre's disease is idiopathic sclerodegenerative disease of conducting system.
- Lev's disease is calcification and sclerosis of conducting system.

Clinical Features

- Regular and slow pulse (30–40/minute)	- Varying intensity of first heart sound
- High volume pulse	- Stokes–Adams attacks
- Irregular cannon waves on JVP	

- The ECG shows constant P–P and R–R intervals but with complete AV dissociation, i.e. the atria and ventricles beat independently and there is no relation between the P waves and the QRS complexes.

Management

- Complete heart block complicating acute inferior myocardial infarction usually does not require any treatment. If the patient deteriorates clinically, it may be treated with intravenous atropine (0.6 mg) that may be repeated every 3–5 minutes for a total of 3 mg. Doses of atropine <0.6 mg may paradoxically result in further slowing of the heart rate.
- If bradycardia is unresponsive to atropine, intravenous infusion of β-adrenergic agonists with rate-accelerating effects (dopamine, epinephrine) or transcutaneous pacing can be effective while the patient is prepared for emergent transvenous temporary pacing.
- However, administration of atropine or other drugs should not delay implementation of external pacing for patients with poor perfusion (e.g. bradycardia causing shock, altered level of consciousness, acute heart failure or ischaemic chest pain).
- Complete heart block complicating acute anterior myocardial infarction should be treated by immediate insertion of temporary pacemaker.
- Chronic complete heart block should be treated by the implantation of a permanent pacemaker.

Q. What are Adams–Stokes attacks (Stokes–Adams–Morgagni attacks)? Write their clinical features.

- An episode of syncope caused by bradycardia related to AV block is called Stokes–Adams–Morgagni syndrome. These commonly occur due to an underlying Mobitz type II block or complete heart block in distal conduction system. Even though VT can also produce loss of consciousness, it is not typically included under Adams–Stokes attack.
- Clinical features
  - Some patients describe a prodrome preceding the attack.
  - Rapid loss of consciousness and the patient may fall, followed by rapid recovery.
  - Convulsions and later death may result if the asystole or severe bradycardia is prolonged to more than 10 seconds.
  - The colour of the skin is pale initially and a characteristic flush appears later when the heart starts beating. In prolonged bradycardia, pallor may give way to cyanosis.

Q. Briefly describe defibrillation and cardioversion.

- Concept
  - The heart is depolarised completely by the passage of an electrical current through it. This is followed by a short period of asystole, following which normal sinus rhythm is resumed.

- Cardioversion is a broad term and includes defibrillation that is used when cardioversion is used in a patient with VF.
- Method
  - Defibrillators using direct current are used for this. An electric shock of high energy but short duration is delivered to the heart through the chest wall, using two electrodes. One electrode is applied over the sternum and the other over the left infrascapular area or in the left axilla. The timing of the electrical discharge should be synchronised with the R wave of the ECG except in VF where unsynchronised defibrillation is required.
- Indications

• Ventricular fibrillation	• Atrial flutter
• Ventricular tachycardia	• Supraventricular tachycardia
• Atrial fibrillation	

- Precautions
  - Patient should be anaesthetised or sedated in elective cardioversion.
  - Digitalis therapy should be withdrawn at least 36 hours before cardioversion.
  - Patients with long-standing atrial arrhythmias should be anticoagulated for at least 3 weeks before cardioversion.

Q. Define acute circulatory failure/shock.

Q. Give the classification, causes and management of shock.

Q. Give the causes and management of cardiogenic shock.

Q. Describe hypovolaemic shock, septic shock, SIRS and sepsis.

Q. Give a brief account of anaphylactic shock and neurogenic shock.

Q. Explain briefly about sympathomimetic amines and vasopressor agents.

Q. Write a note on adrenergic receptors.

Definition

- Shock (acute circulatory failure; low-output state) is defined as a state in which severe reduction in tissue perfusion leads first to reversible, and then, if prolonged, to irreversible cellular injury. The cellular injury caused by inadequate delivery of oxygen and substrates also induces production of inflammatory mediators that further compromise perfusion.
- Basic derangement in shock is inadequate cardiac output with compensatory vasoconstriction and tissue hypoperfusion.
- Cardiogenic shock is a clinical condition of inadequate tissue perfusion due to cardiac dysfunction. The definition of cardiogenic shock includes haemodynamic parameters: Persistent hypotension (systolic blood pressure <90 mmHg or mean arterial pressure 30 mmHg lower than baseline) with severe reduction in cardiac index (<1.8 L/minute/m^2 without support or <2.0–2.2 L/minute/m^2 with support), and adequate or elevated filling pressure (e.g. left ventricular end-diastolic pressure >18 mmHg or right ventricular end-diastolic pressure >10–15 mmHg).

Classification and Causes

- The common types of shocks and their causes are given in the information box.

Type of shock	Causes
• Hypovolaemic shock	Haemorrhage, severe vomiting and diarrhoea, plasma loss in burns and acute pancreatitis, diabetic ketoacidosis
• Cardiogenic shock	Acute myocardial infarction (when more than 40% of myocardium is damaged), acute aortic regurgitation, acute mitral regurgitation, rupture of interventricular septum, myocarditis, rupture of papillary muscle, right ventricular infarction with excessive diuretic therapy, acute massive pulmonary embolism, cardiac arrhythmias, dilated cardiomyopathy, pericardial tamponade, cardiac tumours, takotsubo cardiomyopathy
• Septic shock	Gram-positive and gram-negative bacterial infections, other infections
• Anaphylactic shock	Drugs, insect stings (see anaphylaxis)
• Neurogenic shock	High cervical cord injury, severe head injury

Terms Used in Relation to Conditions with Systemic Inflammation

Term	Definition
• Infection	An inflammatory response to micro-organisms or invasion of normally sterile host tissue by micro-organisms
• Bacteraemia	Presence of viable bacteria in the blood
• Systemic inflammatory response syndrome (SIRS)	Systemic inflammatory response to a variety of insults manifested by two or more of the following: • Temperature >38°C or <36°C • Heart rate >90 beats/minute • Respiratory rate >20/minute or $PaCO_2$ <32 mmHg • TLC count >12,000/mm^3 or <4000/mm^3 or >10% immature cells
• Sepsis	SIRS due to infection
• Severe sepsis	Sepsis associated with organ dysfunction, hypoperfusion or hypotension (may manifest as lactic acidosis, oliguria, acute alteration in mental status)
• Septic shock	Sepsis-induced hypotension despite adequate fluid resuscitation along with perfusion abnormalities (including lactic acidosis, oliguria and acute alteration in mental status). Patients whose blood pressure is supported on inotropics are also considered to be in septic shock
• Multiple organ dysfunction syndrome (MODS)	Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained
• Acute respiratory distress syndrome (ARDS)	See discussion on ARDS

Pathophysiology

Sympathoadrenal and Neuroendocrine Responses

- Stimulation of baroreceptors and chemoreceptors by hypotension leads to increased sympathetic activity.
- This is augmented by release of catecholamines from the adrenals.
- These changes produce increased myocardial contractility, tachycardia and vasoconstriction resulting in partial restoration of blood pressure.
- Reduction in blood flow to kidneys stimulates release of renin that ultimately results in enhanced production of aldosterone (via angiotensin I and II). This causes sodium and water retention.
- During shock there is increased release of antidiuretic hormone and cortisol that helps in retaining fluid and sodium.
- All these effects try to restore blood pressure but at the expense of reduced perfusion to vital organs such as kidneys. If shock is not treated in the early stage, these responses can no longer maintain the blood pressure and a stage of irreversible shock develops.

Inflammatory Reaction

- This occurs in patients with all types of shock but is more apparent in sepsis.
- There is activation of leucocytes and release of a variety of potentially damaging mediators.
- Endotoxin (a lipopolysaccharide) released by gram-negative bacteria is a potent trigger of inflammatory response.
- There is a release of cytokines (important being tumour necrosis factor-α, interleukin-1 and interleukin-10), activation of complement components, release of platelet activating factors, prostaglandins and leucotrienes. TNF-α and IL-6 have myocardial depressant action. TNF-α also induces coronary endothelial dysfunction, which may further diminish coronary flow in patients with cardiogenic shock.
- Endothelial cells also play a role in sepsis-induced shock as they produce increased amount of nitric oxide synthase. This enzyme increases the production of nitric oxide, a potent vasodilator that may contribute to prolonged shock and reduced reactivity to adrenergic agents.

Neurogenic Shock

- Neurogenic shock is caused by the loss of sympathetic control of resistance vessels resulting in massive dilatation of arterioles and venules. Pooling of blood in venous system leads to reduced venous return to heart, which produces fall in stroke volume, cardiac output and blood pressure. Arteriolar dilatation reduces blood pressure further.

Cardinal Features of Shock

- Hypotension with a systolic blood pressure <90 mmHg
- Tachycardia (> 100/minute) with thready pulse
- Cold, clammy skin
- Peripheral cyanosis often present
- Tachypnoea, Cheyne–Stokes breathing
- Altered mental status
- Urine output <30 mL/hour
- Hyperlactatemia indicating abnormal cellular oxygen metabolism (lactate >1.5 mmol/L)

Note

- Some patients with septic shock may initially present with warm hyperperfused extremities ("warm shock") due to abnormal peripheral vasodilatation.
- Specific clinical manifestations of the underlying cause of shock are usually present.
- In neurogenic shock the extremities are often warm due to arteriolar dilatation.

Pathophysiology and Clinical Manifestations of Shock
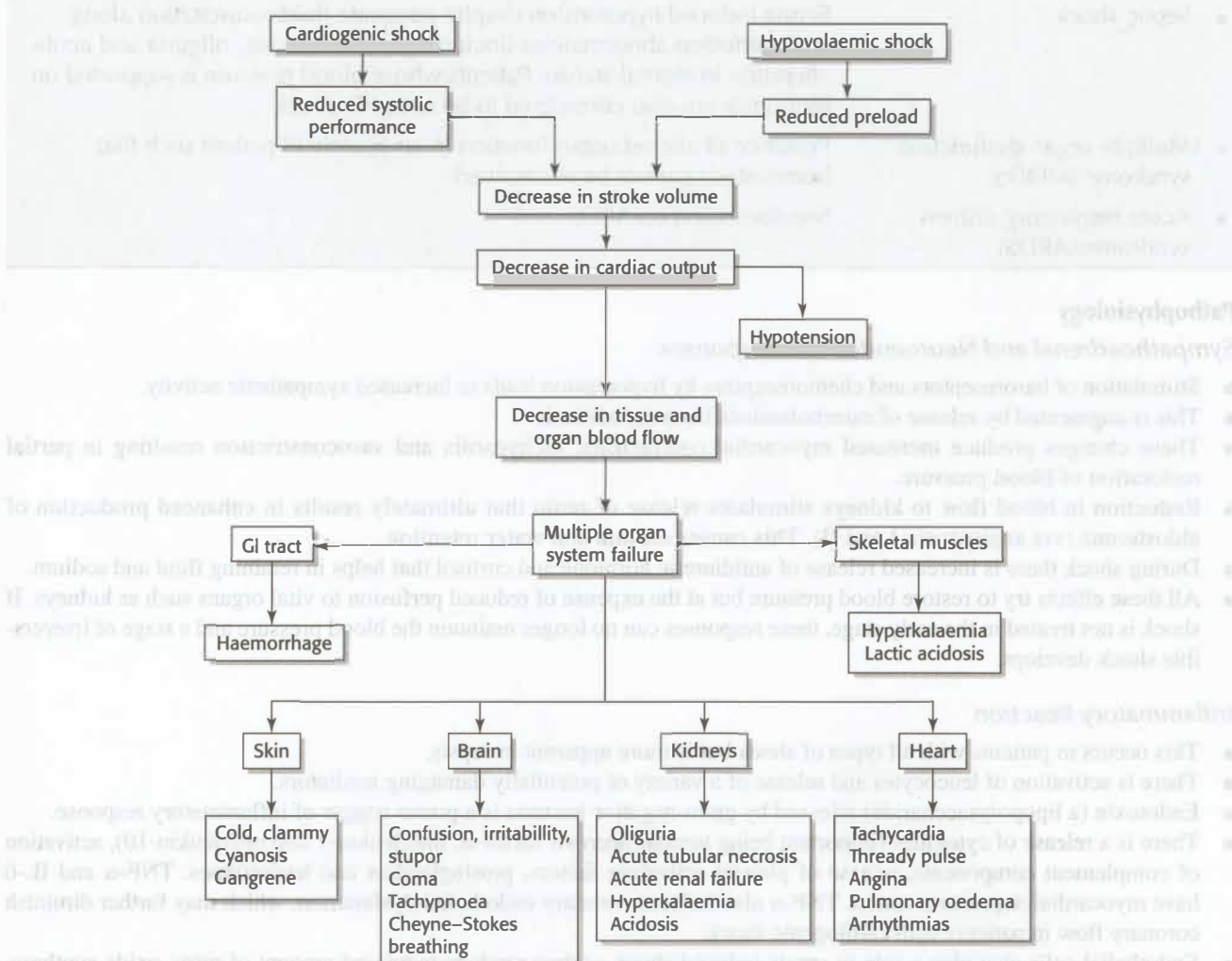
Management of Shock

- Management of shock can be discussed under three headings:
  - Patient monitoring
  - General measures
  - Vasopressors and inotropes (sympathomimetic amines and vasopressin)

- Note that these measures are applicable to all shock syndromes. Special considerations in specific shock syndromes will be discussed later.

Patient Monitoring

- Clinical monitoring of pulse, blood pressure and respiration.
- Electrocardiographic monitoring for cardiac rate, rhythm and arrhythmias.
- Arterial blood gases and pH for correction of acidosis and hypoxia.
- Central venous pressure monitoring for knowing the absolute and relative blood volume, and for guiding fluid replacement. This is particularly useful in the management of hypovolaemic shock.
- Pulmonary capillary wedge pressure monitoring with a Swan–Ganz catheter in the management of cardiogenic shock.
- Urinary catheterisation to monitor hourly urinary output.
- Arterial catheterisation for monitoring arterial pressure.

General Measures

- Care of the skin, airway, bowel and bladder, and nutrition.
- Pain and anxiety should be alleviated by re-assurance .
- Patient should be put in a horizontal position with legs slightly elevated, unless this position is uncomfortable or causes shortness of breath. In that case, he should be allowed the most comfortable position (e.g. propped up).
- Correction of hypovolaemia.
  - Correction is based on the amount and nature of fluid lost, clinical state of the patient and central venous pressure or pulmonary artery wedge pressure (PAWP).
  - Hypovolaemia is corrected by blood, Ringer's lactate solution, isotonic saline solution, dextran, albumin or plasma, depending on the situation.
- Prevention and treatment of renal complications.
  - In the initial stages of shock there is renal vasoconstriction that if prolonged can lead to acute tubular necrosis and renal failure. Protection of the kidneys from vasoconstriction can be achieved by one of the following measures, after a rapid and adequate correction of hypovolaemia:
    - Inducing diuresis with furosemide
    - Inducing diuresis with mannitol
    - Intravenous low-dose (2–4 μg/kg/minute) dopamine has a vasodilator effect on renal vessels.

  Note: None of these methods have been found to be of much use; however, most physicians still use them.
  - Once acute tubular necrosis and renal failure have set in the patient, should be managed as for acute renal failure.
- Correction of hypoxia with oxygen by face masks or nasal prongs, and if necessary, by intubation and mechanical ventilation.
- Correction of acidosis with intravenous sodium bicarbonate (if acidosis is severe).
- Treatment of cardiac arrhythmias with drugs, electrical cardioversion or pacing.
- Treatment of sepsis (especially in septic shock) with antibiotics and drainage of any abscesses.
- Low-dose corticosteroids are recommended in early stages of septic shock.

Vasopressors and Inotropic Agents

Sympathomimetic Amines

- These agents must be used only after correcting volume deficit.
- Sympathomimetic amines act by increasing the cardiac output (by increasing myocardial contractility and heart rate) and selective vasoconstriction.
- By these two effects they raise the arterial pressure allowing better perfusion of ischaemic regions. This is accomplished by redistribution of blood flow to vital organs like kidneys, heart and brain, but away from skin and skeletal muscle.
- Main guidelines while using sympathomimetic amines should be elevation of arterial systolic blood pressure to levels between 110 and 120 mmHg, and maintaining a urinary output of more than 30 mL/hour.
- Dobutamine is primarily an inotropic agent as it mainly increases the myocardial contractility.
- For a better understanding of the actions of sympathomimetic amines one should be familiar with the adrenergic receptors and the pharmacokinetics of the drugs.

Adrenergic Receptors

Receptors	Site	Action
• α (vascular)	Arterioles	Vasoconstriction
	Venules	
	Veins	
• β-1 (cardiac)	Myocardium	Increase contraction
	Sinoatrial node	Increase heart rate
	AV node	Increase AV conduction
• β-2 (vascular)	Arterioles	Vasodilatation
	Lungs	Bronchial dilatation

Commonly Used Sympathomimetic Amines

Amine (dose)	Receptor activated	Actions
• Dopamine		
• 3 μg/kg/minute	Dopaminergic	Vasodilator action on renal, mesenteric, cerebral and coronary
• 3–10 μg/kg/minute	β-1	vessels
• > 10 μg/kg/minute	α	Increase myocardial contractility, heart rate and cardiac output
		Vasoconstriction
• Dobutamine		
• 1–10 μg/kg/minute	β-1	Marked increase in myocardial contractility with minimal increase in heart rate and minimal vasodilatation of peripheral vessels
• Noradrenaline		
• 2–8 μg/minute	β-1	Increased myocardial contractility, heart rate and cardiac output
	α	Vasoconstriction in skin, muscle and splanchnic beds
	β-2	Coronary vasodilatation
• Adrenaline		
• 1–8 μg/minute	β-1	Increased myocardial contractility, heart rate and cardiac output
	α	Vasoconstriction in most vessels except skeletal muscles and coronaries
	β-2	Vasodilatation in skeletal muscles and coronaries
• Isoproterenol		
• 1–4 μg/minute	β-1	Increased myocardial contractility, heart rate and cardiac output
	β-2	Vasodilatation predominantly in skeletal muscles
• Phenylephrine		
• 20–200 μg/minute	α	Vasoconstriction

• In general, noradrenaline is the first vasopressor of choice. If an additional agent is required, adrenaline or dopamine is added. Dobutamine alone is useful to augment cardiac output if arterial pressure is near-normal. Otherwise, noradrenaline or a combination of dopamine and dobutamine is preferred as initial sympathomimetic agents in cardiogenic shock.

Vasopressin
• Vasopressin is a hormone synthesised in hypothalamus and then transported to and stored in pituitary gland.
• It is released in response to decreased blood volume, decreased intravascular volume and increased plasma osmolality.

- Vasopressin constricts vascular smooth muscle directly via V_1 receptors, and also increases responsiveness of the vasculature to catecholamines.
- Vasopressin may also increase blood pressure by inhibition of vascular smooth muscle nitric oxide production.
- Addition of a low dose of vasopressin (0.01 to 0.04 U/minute) to sympathomimetic catecholamines can raise blood pressure in patients with pressor-refractory septic shock.

Special Considerations in Specific Shock Syndromes

Cardiogenic Shock

- Establish large bore peripheral intravenous access.
- Correct any bradyarrhythmia (with atropine/temporary pacing) or tachyarrhythmia (with cardioversion), which may be contributing to hypotension.
- Insert a peripheral arterial line to monitor blood pressure and a urinary catheter.
- If clinical signs or haemodynamic monitoring indicates that the left ventricle is under filled (PCWP <15 mmHg), infuse 100–200 ml boluses of intravenous fluid to optimise left ventricular filling pressures (aiming for PCWP of approximately 15 mmHg).
- If PCWP >18 mmHg, do not infuse intravenous fluid.
- Give diuretics in conjunction with inotropes (to prevent further hypotension).
- Commonly used vasopressors are dobutamine and dopamine. Less commonly used are noradrenaline, milrinone and enoximone.
- Antithrombotic therapy with aspirin and heparin should be given in patients with acute MI. Clopidogrel may be deferred until after emergency angiography, because on the basis of angiographic findings, coronary artery bypass grafting may be performed immediately.
- Vasodilator therapy (in selected cases).
  - Venodilatation reduces central venous pressure and right ventricular output, and slows the accumulation of pulmonary oedema.
  - Arteriolar dilatation improves left ventricular function by reducing the afterload.
  - Commonly used agents are nitroglycerine and nitroprusside.
- Circulatory assist devices
  - Circulatory assist devices may be beneficial in selected cases of cardiogenic shock. The various modalities include:
    - Intra-aortic balloon counterpulsation (use of an IABP improves coronary and peripheral perfusion via diastolic balloon inflation and augments left ventricle performance via systolic balloon deflation with an acute decrease in afterload).
    - Partial cardiac bypass (left ventricle assist devices)
    - Extracorporeal membrane oxygenator (ECMO)
- Percutaneous coronary interventions (PCI) and thrombolytic therapy in selected cases of acute myocardial infarction (see "acute ST-elevation myocardial infarction"). Thrombolytic therapy is less effective but is indicated when PCI is impossible or if a delay has occurred in transport for PCI, and when MI and cardiogenic shock onset is within 3 hours.
- Surgical therapy
  - Role of surgical therapy in cardiogenic shock is mainly aimed at correction of underlying cause. It is indicated in selected cases of cardiogenic shock resulting from the following:
    - Ruptured papillary muscle and acute mitral regurgitation
    - Rupture of the interventricular septum
    - Selected cases of acute aortic regurgitation, aortic dissection and acute massive pulmonary embolism
    - Myocardial infarction (where re-vascularisation is done by either PCI or coronary artery bypass surgery)

Septic Shock (Discussed Elsewhere)

Anaphylactic Shock (Discussed Elsewhere)

Neurogenic Shock

- Horizontal positioning of the patient.
- Maintain an adequate fluid balance. Large amount of fluids may be required.
- Noradrenaline may be required in some cases.

Q. Define pulmonary oedema. Enumerate the causes of pulmonary oedema.

Q. Discuss the aetiology, clinical presentation, investigations and management of cardiogenic pulmonary oedema. Add a note on the pathophysiology.

Aetiology of Pulmonary Oedema

- **Cardiogenic pulmonary oedema** (primary abnormality is elevated pulmonary capillary pressure)

  - Myocardial infarction
  - Hypertensive heart disease (including accelerated hypertension)
  - Mitral stenosis, mitral regurgitation
  - Aortic stenosis, aortic regurgitation
  - Congenital heart diseases
  - Myocarditis

- **Non-cardiogenic pulmonary oedema** (primary abnormality is not elevated pulmonary capillary pressure)
  - Disruption of alveolar-capillary membranes, e.g. ARDS (for causes, refer ARDS)
  - Increased negativity of the interstitial pressure, e.g. rapid evacuation of a large pneumothorax or pleural effusion, and acute severe asthma
  - Impeding lymphatic drainage by lymphatic blockade, e.g. fibrotic and inflammatory diseases of lung and lymphangitis carcinomatosis
  - Precise mechanism is unknown, e.g. narcotic overdose (morphine, methadone, dextropropoxyphene), exposure to high altitude and neurogenic pulmonary oedema

- Cardiogenic pulmonary oedema can also be classified as follows:

- Hypertensive pulmonary oedema presents with signs and symptoms of heart failure accompanied by high blood pressure (systolic >140 mmHg) and relatively preserved left ventricular function with a chest radiograph compatible with acute pulmonary oedema. These patients are often euvolaemic.

- Normotensive pulmonary oedema patients have normal blood pressure, volume overload with or without reduced left ventricular function.

- Hypotensive pulmonary oedema patients have cardiogenic shock with markedly depressed left ventricular function and pulmonary oedema.

Pathophysiology of Cardiogenic Pulmonary Oedema

- Cardiogenic pulmonary oedema is transudation of fluid, macromolecules and red blood cells from the pulmonary capillaries into initially the interstitium and later into alveoli and bronchioles.
- Normally pulmonary interstitium is efficiently drained by lymphatics. In pulmonary oedema the rate of fluid accumulation in the interstitium exceeds the drainage capacity of lymphatics, which results in accumulation of fluid in the interstitium.
- Various factors that operate in the development of pulmonary oedema can be summarised as follows:
  - Elevated pulmonary capillary pressure favouring transudation of fluid.
  - Widening of the pulmonary capillary endothelial intercellular junctions, allowing passage of fluid, macromolecules and red blood cells into the interstitium (interstitial oedema).
  - Disruption of the intercellular junctions between the alveolar lining cells, allowing fluid, macromolecules and red blood cells to enter the alveoli (alveolar oedema).

Stages in Development

- "Interstitial oedema"—This is the early stage where oedema is confined to interstitium.
- "Alveolar oedema"—This occurs later, with oedema fluid, macromolecules and red blood cells entering the alveoli.

Clinical Features of Acute Pulmonary Oedema

- Severe dyspnoea and orthopnoea
- Cough that is initially dry, but later with copious, pinkish, frothy expectoration
- Anxiety, pallor, sweating, cyanosis
- Tachycardia, tachypnoea

- Cold, bluish extremities
- Bilateral scattered rhonchi
- Bilateral crepitations, predominantly basal
- Signs of underlying heart disease
- Without effective treatment, there is progressive hypoxia, hypercapnia and acidosis. Eventually, patient dies of respiratory arrest.

Investigations

- Arterial blood gas studies show hypoxia. Initially, the patient has hypocapnia but in late stages hypercapnia develops.

Radiological Features of Acute Pulmonary Oedema

Radiological grading of pulmonary oedema	
- Grade 1	- Prominence of the upper lobe veins (reverse moustache sign; stag's antlers sign)
- Grade 2 (interstitial oedema)	- Kerley A lines—thin non-branching lines radiating from the hilum
	- Kerley B lines—transverse thin lines of 1–3 cm, seen at the lung bases, lying perpendicular to the pleura
	- Blurring of the outline of the central pulmonary vessels and hilum due to perivascular oedema
	- "Endobronchial cuffing"—blurring seen around the end-on view of bronchi
- Grade 3 (alveolar oedema)	- Bilateral fluffy shadows in the lung fields
	- Confluencing of fluffy shadows around hilum giving the "bat's wing" appearance (bilateral perihilar opacity dense at the hilum, fading towards periphery)
	- Pleural effusions at uncommon sites like lamellar effusion, interlobar effusion and subpulmonic effusion. Interlobar effusion might give the appearance of a tumour, but it disappears with treatment (hence called "phantom", "disappearing" or "vanishing" tumour)

Treatment of Acute Cardiogenic Pulmonary Oedema

- Propped-up position or sitting position with legs hanging down along the side of the bed to reduce venous return.
- Oxygenation:
  - 100% oxygen, preferably under positive pressure. Oxygen corrects hypoxia and positive pressure raises intra-alveolar pressure reducing transudation of fluid.
  - Non-invasive ventilation (NIV) may be tried if oxygen saturation remains below 90%. NIV can be provided by either CPAP (continuous positive airway pressure) or bilevel ventilation (both inspiratory and expiratory support, BiPAP). NIV augments cardiac output, decreases left ventricular afterload, increases functional residual capacity and respiratory mechanics, and reduces work of breathing.
- Morphine 2–5 mg intravenously slowly, and repeated if necessary, reduces anxiety and reduces venous return.
- Intravenous loop diuretics, e.g. furosemide 40–100 mg (drug of choice), ethacrynic acid 40–100 mg or bumetanide 1 mg.
  - By diuresis, they reduce the circulating blood volume and hasten the relief of pulmonary oedema.
  - Intravenous furosemide has a venodilator action by which it reduces venous return. This effect occurs within a few minutes while diuresis may take 30 minutes.
  - Diuretics should be avoided in hypertensive pulmonary oedema as patients are usually euvolaemic or even hypovolaemic.
- Vasodilators:
  - Preload reduction with nitrates sublingually (5–10 mg of isosorbide dinitrate) or nitroglycerine intravenously (5–100 μg/minute as infusion). Initial recommended dose of nitroglycerine is 10–20 μg/minute, and it is increased in increments of 5 μg/minute every 3–5 minute as needed. Tachyphylaxis is common, necessitating incremental dosing. Major adverse effects of nitrates are hypotension, tachycardia and headache.

- Afterload reduction with intravenous sodium nitroprusside 20--30 μg/minute in patients with systolic blood pressure more than 100 mmHg. Nitroprusside is particularly useful in settings in which acute afterload reduction is needed, including hypertensive emergency, acute aortic regurgitation, acute mitral regurgitation and acute ventricular septal defect. The major complication of nitroprusside therapy is hypotension and toxicity due to accumulation of cyanide or thiocyanate. This usually occurs only in patients who have been receiving high doses of nitroprusside for 24 hours or more, commonly in patients with renal failure.
- Nesiritide, a recombinant form of human B-type natriuretic peptide (BNP), is a venous and arterial vasodilator that may also potentiate the effect of diuretics. It is given intravenously as a 2 μg/kg bolus followed by a 0.01 μg/kg/minute infusion. Hypotension and worsening of renal functions are important side effects.
- Inotropic agents: To increase the contractility of the myocardium, inotropic agents have been useful in hypotensive pulmonary oedema or cardiogenic shock. Intravenous dopamine or dobutamine are most often used for this purpose. Norepinephrine may be used if there is no response.
  - Dobutamine is useful in patients with pulmonary oedema with normal or low-normal blood pressure.
  - Dopamine is preferred to dobutamine, if shock is also present.
  - Intravenous digitalis has no role in pulmonary oedema; however, in presence of supraventricular tachycardia with fast ventricular rate intravenous digoxin (0.5 mg) may be useful.
  - Milrinone increases the contractile state of the heart and reduces the systemic vascular resistance, both of which decrease the left ventricular afterload and filling pressures. The loading dose is 50 μg/kg over 10 minutes followed by a maintenance dose of 0.375–0.5 μg/minute. However, it is not recommended at present as it increases risk of life-threatening arrhythmias.
  - Levosimendan, a novel calcium sensitizer that improves cardiac contractility by binding to troponin-C in cardio-myocytes and has vasodilatory properties, has beneficial haemodynamic and clinical effects in patients with acute pulmonary oedema.
- Intravenous aminophylline 250--500 mg diminishes bronchoconstriction, increases renal blood flow and sodium excretion (by diuresis), and increases myocardial contractility.
- Monitoring the intra-arterial pressure and pulmonary vascular pressures through a Swan–Ganz catheter in selected cases.
- In refractory cases rotating tourniquets may be applied to the limbs. Tourniquets with pressure just above the diastolic are applied to three of the four limbs and rotated every 15 minutes. However, their efficacy is unproven.
- Ultrafiltration (a method of fluid removal) may be useful in patients with renal dysfunction and expected diuretic resistance.
- Correction of precipitating causes like infection or arrhythmias.
- Treatment of underlying cause.

Q. Define orthopnoea, trepopnoea and platypnoea.

- Orthopnoea
  - Dyspnoea that develops in recumbent position and is relieved by sitting up.
  - Occurs within a few minutes of assuming recumbent position.
  - Occurs in left heart failure.
- Platypnoea
  - Dyspnoea that develops in upright position and gets relieved in supine position.
  - Occurs in left atrial thrombus, left atrial myxoma and pulmonary arteriovenous fistula.
- Trepopnoea
  - Dyspnoea that occurs only in left or right lateral decubitus position.
  - May occur in patients with pathology of one lung and chronic congestive heart failure.

Q. Define heart failure. Discuss the types, common causes, pathophysiology, clinical features and management of heart failure.

Definition

- Heart failure or cardiac failure is defined as a state in which the ventricles at normal filling pressures (i.e. adequate intravascular volume) cannot maintain an adequate cardiac output to meet the metabolic needs of peripheral tissues or can do so only with an elevated filling pressure. It results from any structural or functional impairment of ventricular filling or ejection of blood.

- The term heart failure is preferred over the older term congestive heart failure because not all patients with heart failure have volume overload.

Pathophysiology

Concept of Preload, Afterload and Myocardial Contractility

- Preload—Refers to the pressure that fills the left ventricle during diastole. It is measured either directly as the left-ventricular end-diastolic pressure, or indirectly and more commonly as the pulmonary artery wedge pressure (PAWP). Main determinants of preload are left ventricular compliance and venous return

- Afterload—Refers to the pressure against which the left ventricle contracts and is measured as the mean aortic pressure. Main determinants of afterload are total peripheral resistance and left ventricle size

- Myocardial contractility (inotropic state)—This mainly depends on the adrenergic nervous activity and the levels of circulating catecholamines

- Heart failure is characterised by a decrease in cardiac output (except in high-output failure). Cardiac output in turn is a function of preload, afterload and myocardial contractility. In heart failure, preload is increased, afterload is increased and myocardial contractility is decreased.
- In the initial stages of heart failure, reduction in cardiac output produces certain compensatory mechanisms. These compensatory mechanisms are initially beneficial, but later become counterproductive and account for most of the manifestations of heart failure. These compensatory mechanisms are mediated through renin–angiotensin system and autonomic nervous system. These mechanisms are discussed below.
  - Increased myocardial contractility: As the ventricle dilates (resulting in increased preload) the ventricular contractility increases resulting in relatively increased volume of blood ejected (Frank–Starling law). However, there is a limit to which the myocardial cells can be stretched so as to enhance their contractility and beyond this limit, their contractility diminishes. The increased left ventricular filling pressures are transmitted to the pulmonary veins that result in alveolar transudation of fluid and pulmonary congestion. Finally, oxygen demand is enhanced due to increased contractility.
  - Myocardial hypertrophy occurs due to volume and pressure overload in the ventricle and helps in enhanced contractility and hence increased cardiac output. However, it produces increased oxygen demand and reduced compliance of the ventricle that results in increased preload that is again transmitted to the pulmonary vasculature.
  - Sympathetic stimulation results in peripheral vasoconstriction that in turn leads to salt and water retention due to direct and indirect effects on the renin–angiotensin system. Sympathetic stimulation also produces increased heart rate and enhances contractility. Increased afterload may be deleterious as it tends to reduce cardiac output and increases oxygen demand of the heart.
  - Myocardial remodelling: The fundamental mechanism that underlies the progressive nature of myocardial dysfunction has been termed remodelling. Important changes in structure and function of the myocardium include hypertrophy and apoptosis (programmed cell death) of myocytes, and alterations in the quantity and composition of extracellular matrix. Remodelling involves not only the ischaemic area but also the viable myocardium, resulting in gradual loss of contractility over a period of time.

Types of Heart Failure

Acute and Chronic Heart Failure

- Acute heart failure develops suddenly. The sudden reduction in cardiac output results in systemic hypotension without peripheral oedema. Best examples are acute myocardial infarction and rupture of a cardiac valve.
- Chronic heart failure develops gradually. Here systemic arterial pressure is well maintained, but oedema accumulates. Best examples are dilated cardiomyopathy and multivalvular disease.
- Compensated heart failure implies that the compensatory changes have prevented the development of overt heart failure. A minor insult like an infection may precipitate severe heart failure.

Low-Output and High-Output Heart Failure

- Low-output heart failure is associated with a low cardiac output. The heart fails to generate adequate output or can do so with high filling pressures. Best examples are heart failure associated with ischaemic heart disease, hypertension, cardiomyopathy, valvular diseases and pericardial disease.
- In high-output heart failure, the heart fails to maintain sufficient circulation despite an increased cardiac output (defined as cardiac output >8 L/minute or a cardiac index >3.9 L/minute/m^2). Best examples are cardiac failure associated with

hyperthyroidism, anaemia, pregnancy, arteriovenous fistulae, beriberi and Paget's disease. The underlying primary physiological problem in high-output heart failure is of reduced systemic vascular resistance. This occurs due to either systemic arteriovenous shunting or peripheral vasodilatation. Both scenarios can lead to a fall in systemic arterial blood pressure, a feature of low-output heart failure. This can lead to sympathetic neural activation, a compensatory rise in cardiac output and neurohormonal activation. This process in turn can cause salt and water retention, and overt clinical heart failure. Thus, salt and water retention, occur both in low- and high-output heart failure due to a similar neurohormonal response to arterial hypotension. In the former it is due to low cardiac output and in the latter due to reduced systemic vascular resistance. In high-output heart failure patients are likely to have warm rather than cold peripheries due to low systemic vascular resistance and peripheral vasodilatation. Right-sided heart failure is prominent in thiamine deficiency (wet beriberi).

Left-Sided, Right-Sided and Biventricular Heart Failure

- "Left side" is a term for the functional unit of left atrium, left ventricle, mitral valve and aortic valve.
- "Right side" is a term for the functional unit of right atrium, right ventricle, tricuspid valve and pulmonary valve.

Left-Sided (Left Ventricular) Heart Failure

- Excess fluid accumulates upstream behind the failing left ventricle.
- There is reduction in left ventricular output, increase in left atrial pressure and increase in pulmonary venous pressure.
  - Acute increase in left atrial pressure causes pulmonary congestion and pulmonary oedema, e.g. myocardial infarction.
  - Gradual increase in left atrial pressure causes reflex pulmonary hypertension but no pulmonary oedema, e.g. aortic stenosis.

Right-Sided (Right Ventricular) Heart Failure

- Excess fluid accumulates upstream behind the failing right ventricle.
- There is reduction in right ventricular output that results in systemic venous congestion.
- Best examples are cor pulmonale, pulmonary valvular stenosis and multiple pulmonary emboli.

Biventricular Heart Failure

- There is failure of both left and right ventricles.
- Best examples are:
  a. Disease processes affecting both ventricles like dilated cardiomyopathy and ischaemic heart disease.
  b. Diseases of left heart leading to chronic elevation of left atrial pressure, pulmonary hypertension and subsequent right ventricular failure.

Forward and Backward Heart Failure

- Forward heart failure is characterised by decreased cardiac output and inadequate perfusion of organs leading to poor tissue perfusion. Poor renal perfusion results in activation of renin–angiotensin–aldosterone system producing excessive absorption of sodium by renal tubules.
- Backward heart failure is characterised by a normal cardiac output, but marked salt and water retention, and pulmonary and systemic venous congestion.

Systolic and Diastolic Heart Failure

- Systolic heart failure (also known as heart failure with reduced ejection fraction) is characterised by an abnormality of ventricular contraction. The ejection fraction is usually below 40%.
- Diastolic heart failure (also known as heart failure with preserved ejection fraction):
  - Characterised by an impaired ventricular relaxation and increased ventricular stiffness resulting in reduced filling (diastolic dysfunction).
  - Diagnosis of diastolic heart failure is based on three features—signs or symptoms of heart failure (usually dyspnoea), normal LV systolic function and diastolic LV dysfunction (using echocardiography or invasive pulmonary capillary wedge pressure).
  - Certain conditions such as ischaemia, left ventricular hypertrophy, hypertension and aortic stenosis predispose to diastolic dysfunction.
  - Survival similar to systolic heart failure.
  - ACE inhibitors, angiotensin receptor blockers and β-blockers do not offer significant benefit in outcome.
- The symptoms of CHF may be identical whether failure is secondary to systolic or diastolic dysfunction.

Risk Factors for Heart Failure

- Hypertension
- Diabetes mellitus
- Use of cardiotoxic substances (e.g. alcohol, tobacco and cocaine)
- Hyperlipidaemia

- Thyroid disorders
- Persistent tachycardia
- Coronary artery disease

Common Causes of Heart Failure

Pressure overload of ventricle
- Systemic hypertension
- Pulmonary hypertension
- Aortic stenosis
- Pulmonary stenosis

Volume overload of ventricle
- Conditions associated with increased metabolic demand
- Mitral regurgitation
- Aortic regurgitation
- Ventricular septal defect
- Patent ductus arteriosus
- Atrial septal defect

Inflow obstruction of ventricle
- Mitral stenosis
- Tricuspid stenosis
- Endomyocardial fibrosis

Impaired ventricular function
- Diffuse myocardial disease
  - Myocarditis
  - Cardiomyopathy
- Segmental myocardial disease
- Myocardial infarction (ischaemic heart disease)

- In practice, the most commonly encountered causes of heart failure are ischaemic heart disease, hypertensive heart disease and valvular heart diseases.

Precipitating and Aggravating Causes of Heart Failure

- Infections
- Anaemia, pregnancy, thyrotoxicosis
- Cardiac arrhythmias
- Supervening heart diseases like myocarditis, infective endocarditis, myocardial infarction
- Systemic hypertension

- Pulmonary embolism
- Drugs like β-blockers, disopyramide, corticosteroids and NSAIDs
- Excess salt intake
- Physical and emotional stress
- Poor compliance with therapy

Clinical Manifestations of Heart Failure

Dyspnoea

- Dyspnoea is initially exertional, but progressively worsens to a stage of breathlessness even at rest.
- The mechanisms underlying dyspnoea include:
  - Interstitial pulmonary oedema surrounding the pulmonary capillaries stimulates the juxtacapillary receptors (J receptors). This elicits a reflexly mediated, "rapid and shallow breathing" of cardiac dyspnoea.
  - Respiratory muscle fatigue
  - Bronchial mucosal oedema
  - Increased bronchial mucus production

Orthopnoea

- Dyspnoea occurring soon after lying flat and relieved by sitting up is known as orthopnoea.
- Nocturnal cough has the same significance as orthopnoea.
- The mechanisms underlying orthopnoea include—in the lying down posture—the following
  - Increased venous return from the lower limbs and abdomen to the lungs
  - Elevation of the diaphragm
  - Reabsorption of the peripheral oedema that had accumulated while ambulant

Paroxysmal Nocturnal Dyspnoea (PND)

- This is an attack of severe shortness of breath and coughing usually occurring at night, awakening the patient from sleep. Paroxysmal nocturnal dyspnoea (PND) persists even after sitting upright whereas simple orthopnoea is relieved by sitting upright.
- Mechanisms underlying PND include:
  - Depression of the respiratory centre during sleep
  - Reduced adrenergic stimulation of the myocardium at night resulting in further impairment of myocardial function
  - In addition, mechanisms causing orthopnoea also contribute to PND

Cardiac Asthma

- This is closely related to PND and nocturnal cough. It is characterised by wheezing secondary to bronchospasm, most prominent at night. Acute pulmonary oedema is a severe form of cardiac asthma.
- The classic explanation for wheezing in heart failure is that it is caused by pulmonary oedema and accompanying bronchial wall oedema. However, it is now thought to be caused by bronchial hyper-reactivity.

Acute Pulmonary Oedema

- It is a severe form of cardiac asthma resulting from marked elevation of pulmonary capillary pressure leading to alveolar oedema.
- Clinically, it is characterised by severe breathlessness, cough with copious, pinkish frothy expectoration and bilateral crepitations.

Cheyne–Stokes Respiration

- A type of periodic breathing with alternate periods of apnoea and hyperventilation seen in advanced heart failure.
- Mechanisms underlying Cheyne–Stokes respiration include:
  - Diminished sensitivity of the respiratory centre to arterial PCO_2 is the main mechanism.
  - Prolongation of the circulation time from lungs to brain that occurs in heart failure.

Nocturia

- A feature of early heart failure.
- Underlying mechanism is a better renal perfusion and diuresis at night when the patient is supine.

Cerebral Symptoms

- Confusion, difficulty in concentration, memory impairment, headache, insomnia and anxiety.
- Underlying mechanisms include:
  - Arterial hypoxaemia
  - Reduced cerebral perfusion

Non-Specific Symptoms

- Fatigue and weakness from reduced perfusion of skeletal muscles
- Low-grade fever from reduction of cutaneous flow
- Anorexia, nausea, abdominal pain and fullness from congestion of liver and portal venous system

Cardiac Oedema

- Due to gravity, cardiac oedema accumulates over dependent parts. In ambulant patients it occurs symmetrically in the legs, particularly in the pretibial region and around the ankles. It is less in the morning and more towards the evening. Oedema is sacral in bedridden patients.
- In advanced stages there is anasarca with oedema fluid accumulating throughout the body. Face and arms are typically spared until the terminal stages.

Cyanosis

- Mainly affects lips and nail beds.
- Extremities are cold and pale due to reduced blood flow, and also cyanosed.

Pulse

- Sinus tachycardia.
- Pulsus alternans is a sign of severe heart failure.

Blood Pressure

- Diminished pulse pressure due to reduced stroke volume.
- Diastolic blood pressure may be slightly raised occasionally, due to generalised vasoconstriction.
- Hypotension is prominent in acute heart failure.

Jugular Venous Pressure

- Jugular venous pressure is raised as a consequence of elevated systemic venous pressure.
- In the early stages jugular venous pressure may not be raised at rest. But it becomes raised:
  - During and immediately after exercise.
  - With sustained pressure on the abdomen (positive hepatojugular or abdominojugular reflux). A positive abdomino-jugular reflux suggests reduced right ventricular compliance so that right ventricle cannot accommodate an increase in venous return.

Third Heart Sound and Fourth Heart Sound

- The presence of a third heart sound in an adult is highly suggestive of heart failure.
- The presence of either of the two (S_3 or S_4) is known as triple rhythm ($S_1 + S_2 + S_3$ or $S_1 + S_2 + S_4$).
- The presence of both of them (S_3 and S_4) is known as quadruple rhythm ($S_1 + S_2 + S_3 + S_4$).
- In some cases, S_3 and S_4 merge to become a single sound that sounds like a triple rhythm, but known as summation gallop.
- The timing of S_1, S_2 and either of S_3 or S_4, in association with an increased heart rate results in a characteristic cadence of a "gallop", when it is known as gallop rhythm (S_3 gallop or S_4 gallop).

Respiratory System

- Inspiratory crepitations over lung bases.
- In patients with pulmonary oedema, crepitations are coarse and heard widely over both lung fields associated with expiratory rhonchi.

Liver (Congestive Hepatomegaly)

- Right upper quadrant pain from stretching of the capsule of the liver.
- Liver is enlarged and tender due to systemic venous hypertension.
- Cardiac cirrhosis occurs in prolonged heart failure which results in atrophy and centrilobular necrosis of liver cells, leading later to extensive fibrosis.
- Hypoglycaemia can occur in long-standing cases due to depletion of liver glycogen stores and increased production of lactic acid from glucose, induced by hypoxia.
- With prolonged hepatomegaly, spleen may also become enlarged.
- Jaundice is a late feature characterised by hyperbilirubinaemia of both conjugated and unconjugated types. In acute hepatic congestion, jaundice is severe and enzymes are markedly elevated.

Pleural Effusion, Ascites and Pericardial Effusion

- Pleural effusion is more common on the right side and results from elevation of pleural capillary pressure and transudation of fluid into pleural space.
- Ascites results from transudation secondary to elevated pressures in hepatic veins, portal veins and veins draining the peritoneum.
- Pericardial effusion can occur rarely.

Kidney

- Oliguria
- Urinary sodium is low, specific gravity is high and contains proteins (less than 1 g/day).
- Prerenal azotaemia is common. Blood urea is typically elevated out of proportion to serum creatinine.

Cardiac Cachexia

- Advanced heart failure is associated with severe anorexia, weight loss and malnutrition.

Haematological Features

- Anaemia in heart failure is common and develops due to a complex interaction of iron deficiency, kidney disease, reduced erythropoietin production and cytokine production. Blood loss may contribute.

Common Diagnostic Studies

- Chest radiograph may show cardiomegaly, prominence of upper lobe veins, Kerley A and B lines, and other features of pulmonary oedema.
  - Prominence of upper lobe veins
  - Kerley B lines—engorged peripheral lymphatics seen in lower lobe
  - Phantom tumour—fluid in horizontal or oblique fissures of lungs; disappears with diuretics
  - "Bat's wing"—increased bronchovascular markings (also known as inverted moustache signs)
  - Pleural effusion (bilateral or unilateral)
  - Cardiomegaly
- Electrocardiography (may show presence of ventricular hypertrophy, atrial abnormality, arrhythmias, conduction abnormalities, previous MI and active ischaemia).
- Brain natriuretic peptide (BNP).
  - Serum levels of BNP and NT-proBNP are elevated in CHF. These tests are highly sensitive for diagnosis of heart failure as the cause of dyspnoea and are often used to differentiate cardiac from respiratory cause of acute dyspnoea in emergency departments. These markers are also used as independent mortality predictors in patients with CHF.
- Assessment of ejection fraction, valvular functions, and chamber size and shape by echocardiography. It can also differentiate between systolic and diastolic heart failure.
- Assessment of ejection fraction by radionuclide ventriculography.
- Exercise stress testing and cardiac catheterisation, if indicated.
- Ambulatory Holter monitoring if arrhythmias are suspected.
- Renal and liver functions as baseline.
- Thyroid function tests to exclude occult thyroid disease.

Management of Heart Failure

- Physical and emotional rest.
  - Absolute bed rest is rarely required.
  - Small doses of tranquillisers may be used.
- Correction of obesity by restriction of caloric intake.
- Salt-restricted diet and avoidance of salt-retaining medicines (e.g. NSAIDs).
  - In mild heart failure, mild sodium restriction
  - In more severe heart failure, more rigid control of sodium intake (1–2 g/day)
  - In severe heart failure, sodium chloride intake should be less than 0.5–1 g/day
  - Restriction of water intake is advised only in most severe cases

Note: Normal diet contains 6-10 g of sodium chloride

- ACE inhibitors (discussed later)—Recommended for all patients with heart failure, whether symptoms are mild, moderate or severe, unless not tolerated or contraindicated.
- β-blockers (discussed later)—Recommended for all patients with CHF (except very severe cases) who remain mildly to moderately symptomatic despite appropriate doses of ACE inhibitors.
- Diuretics (discussed later)—Used if patient has volume overload.

Note: ACE inhibitors and β-blockers reduce mortality in patients with prior MI. ACE inhibitors also reduce occurrence of symptomatic heart failure after MI

- Digoxin—For details regarding digoxin therapy, refer later.
- Aldosterone receptor blockade with spironolactone is recommended for patients who remain severely symptomatic despite appropriate doses of ACE inhibitors and diuretics. Aldosterone promotes fibrosis in the heart and contributes to diastolic stiffness. Spironolactone reduces mortality related to heart failure.

- Vasodilators—For details regarding vasodilator therapy, refer later.
- Sympathomimetic amines—For details regarding sympathomimetic amines, refer "shock".
  - Sympathomimetic amines improve myocardial contractility in heart failure. They are dopamine, dobutamine, adrenaline and isoproterenol (isoprenaline). Of these drugs, dopamine and dobutamine are used in acute or refractory heart failure.
    - Dopamine is useful in heart failure associated with hypotension.
    - Dobutamine (continuous intravenous infusion of 2.5–10 µg/kg/minute) is useful in acute heart failure without hypotension.
  - However, all inotropic agents except digoxin have been associated with excess mortality and should be reserved for patients unresponsive to traditional oral medications for heart failure.
  - Inotropic agents (including milrinone and amrinone) can be used short term to stabilise cardiogenic shock and to allow for other therapies, including re-vascularisation, valve repair or initiation of more traditional therapies. In addition, inotropic agents can be used to bridge a patient to cardiac transplantation or insertion of a left ventricular assist device. Finally, inotropic agents can be used as palliation when heart failure becomes refractory and the patient is not a candidate for either cardiac transplantation or a ventricular assist device.
- Amrinone and milrinone are phosphodiesterase III inhibitors with positive inotropic and vasodilator actions. They act by increasing contractility and dilating systemic vascular bed. Used in hospitalised patients with severe CHF.
- Mechanical removal of fluid by thoracentesis, paracentesis and dialysis are measures used in severe cases.
- Vasopressin antagonists:
  - Elevated levels of vasopressin found in patients with heart failure.
  - Action on V_2 receptors produces water retention and hyponatraemia which increase workload on the heart. Action on V_{1a} receptors causes vasoconstriction, which again increases workload on the heart. Vasopressin also plays a key role in pathological remodeling of myocardium.
  - Tolvaptan, a V_2-receptor antagonist has been shown to be beneficial in heart failure.
- Miscellaneous
  - Anticoagulation therapy is indicated in patients with heart failure who are at risk for thromboembolism (patients with atrial fibrillation, valvular heart disease, documented left ventricular thrombus or a history of embolic stroke). It may also be given in patients with a very low ejection fraction.
  - Angiotensin receptor blockers are also effective and can be used in place of ACE inhibitors if the latter agents cannot be used.
  - Omega-3 polyunsaturated fatty acid (PUFA) supplementation is reasonable to use as adjunctive therapy in patients with NYHA class II–IV symptoms to reduce mortality and cardiovascular hospitalisations.
  - Biventricular pacing and implantable cardioverter defibrillator (ICD) in select group of patients.
    - Consider placement of an ICD to monitor heart rate and rhythm and to correct arrhythmia in patients with left ventricular dysfunction, and an ejection fraction less than 30%.
    - Cardiac re-synchronisation therapy (biventricular pacing) in patients with an ejection fraction <35%, a QRS interval >150 msec and symptoms despite maximum medical therapy.
  - Surgical treatment options include left ventricular aneurysmectomy, left ventricular assist devices and cardiac transplantation.
- The overall management of heart failure is summarised in the flow diagram below.
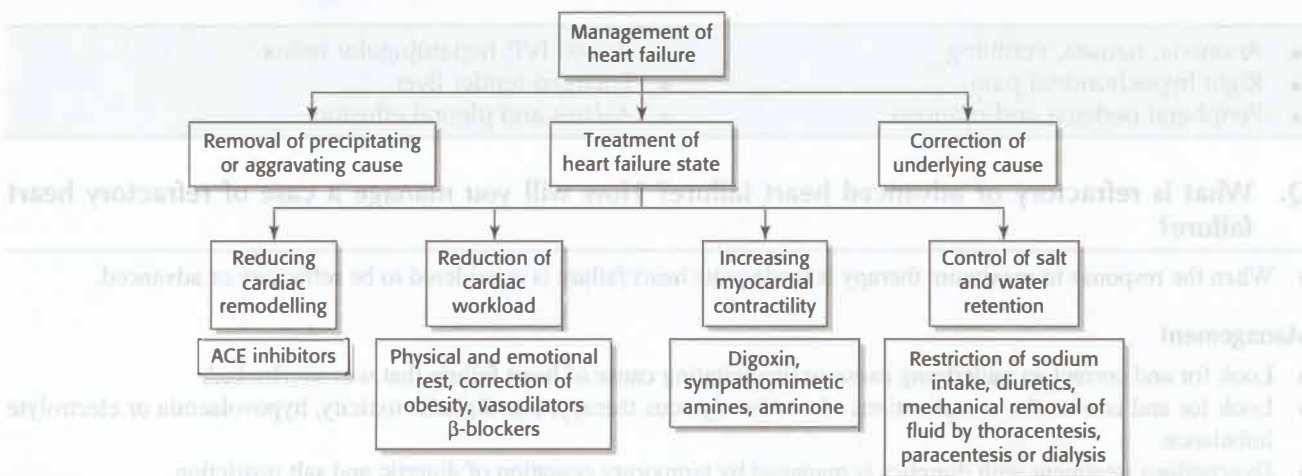
Steps in The Management of Chronic Heart Failure

Functional class I	Functional class II	Functional class III	Functional class IV
• ACE inhibitors • β-blockers	• Mild restriction of activity • Mild sodium restriction • ACE inhibitors • β-blockers • Diuretics (for volume overload) • Digoxin (if symptoms persist) • Aldosterone antagonist (e.g. spironolactone)*	• Moderate restriction of activity • Moderate sodium restriction • Diuretics • Spironolactone • ACE inhibitors • β-blockers • Digoxin • Direct vasodilators (if ACE inhibitors contraindicated or poorly tolerated)	• Severe restriction of activity • Severe sodium restriction • Diuretics • Spironolactone • ACE inhibitors • Digoxin • Intravenous dopamine/ dobutamine and amrinone (if required)

*Note: Patients with NYHA class II heart failure should have a history of prior cardiovascular hospitalisation or elevated plasma natriuretic peptide levels to be considered for aldosterone receptor antagonists.

Q. Discuss the pathogenesis of ascites in congestive heart failure.

- Increase in hepatic venous pressure and portal venous pressure results in transudation of fluid into the peritoneal cavity.
- Decrease in renal perfusion leads to activation of renin–angiotensin–aldosterone system, which in turn is responsible for salt and water retention (contributing to ascites and oedema).
- Congestion of gastrointestinal tract results in diminished appetite and protein intake, leading to hypoproteinaemia (contributing to ascites and oedema).
- Chronic congestive heart failure results in cardiac cirrhosis leading to ascites.

Q. What are the features of left ventricular failure (left-sided failure; left heart failure)?

• Dyspnoea, orthopnoea, • Paroxysmal nocturnal dyspnoea (PND) • Nocturia • Acute pulmonary oedema • Tachypnoea, pallor, sweating	• Pulsus alternans • Narrow pulse pressure • S_3 gallop of left ventricular origin • S_4 gallop • Basal crepitations

Q. What are the features of right ventricular failure (right-sided failure; right heart failure)?

• Anorexia, nausea, vomiting • Right hypochondrial pain • Peripheral oedema and cyanosis	• Raised JVP, hepatojugular reflux • Enlarged tender liver • Ascites and pleural effusion

Q. What is refractory or advanced heart failure? How will you manage a case of refractory heart failure?

- When the response to maximum therapy is inadequate heart failure is considered to be refractory or advanced.

Management

- Look for and correct an underlying cause or precipitating cause of heart failure that was overlooked.
- Look for and correct the complications of overly vigorous therapy, e.g. digitalis toxicity, hypovolaemia or electrolyte imbalance.
- Overzealous treatment with diuretics is managed by temporary cessation of diuretic and salt restriction.

- Hyponatraemia is treated with temporary cessation of diuretic therapy and restriction of oral water intake.
- Intravenous vasodilator (sodium nitroprusside) along with dopamine or dobutamine may be useful in refractory cases.
- Intravenous nesiritide, a recombinant form of BNP is beneficial. It is a potent vasodilator that provides both early and sustained reduction in filling pressures.
- Intravenous amrinone with an angiotensin converting-enzyme inhibitor (ACE inhibitor) in refractory cases.
- Cardiac transplantation to be considered if all the above-mentioned measures fail.
- Experimental agents include endothelin-1 receptor blockers (e.g. tezosentan, a V_2 receptor blocker) and vasopressin receptor blockers (e.g. tolvaptan). Endothelin-1 is a potent vasoconstrictor while vasopressin mediates both vasoconstriction (V_1 receptor) and water retention (V_2 receptor).

Q. Give a brief account of brain natriuretic peptide (BNP).

Pathophysiology

- Cardiac myocardium secretes several natriuretic peptides to maintain stable blood pressure and plasma volume and to prevent excess salt and water retention.
- Atrial natriuretic peptide (ANP) is secreted by the atrial myocardium.
- BNP was initially isolated in porcine brains.
- In humans, BNP is primarily secreted by the ventricles in the heart as a response to left ventricular stretching or wall tension. It is activated only after a prolonged period of volume overload.
- Cardiac myocytes secrete a BNP precursor that is synthesised into proBNP, which consists of 108 amino acids. After it is secreted into the ventricles, proBNP is cleaved into the biologically active C-terminal portion and the biologically inactive N-terminal (NT-proBNP) portion.
- Natriuretic peptides have several actions:
  - Down regulating the sympathetic nervous system
  - Down regulating the renin–angiotensin system
  - Facilitating natriuresis and diuresis through the afferent and efferent haemodynamic mechanisms of the kidney and distal tubules
  - Decreasing peripheral vascular resistance
  - Increasing smooth muscle relaxation

Utility

- Normal values of BNP <50 pg/mL or <50 ng/L.
- BNP levels are used in the diagnosis of congestive heart failure. It can be useful in patients presenting in the emergency room when the clinical diagnosis of heart failure is uncertain.
- Elevated BNP levels also have been associated with renal failure (because of reduced clearance), pulmonary embolism, pulmonary hypertension, chronic hypoxia, atrial fibrillation, acute myocardial infarction, obese patients and sepsis.
- Elevated BNP levels in patients with heart failure may be associated with an increased risk of death or cardiovascular events.
- BNP measurement is a potential tool for monitoring treatment response in patients with heart failure.

Q. Give a brief account of digoxin.

Q. What are the manifestations of digoxin toxicity? How will you manage a case of digoxin toxicity?

- Digoxin is a purified glycoside from the plant *Digitalis lanata*.

Action

- Increases myocardial contractility.
- Prolongs the refractory period of AV node, thereby slowing ventricular rate.
- Reflex vasodilatation from withdrawal of sympathetic constrictor activity in patients with congestive heart failure.

Pharmacokinetics

- Bioavailability of digoxin tablet is 60–80%.
- Plasma contains only 1% of the body stores of digoxin, the rest is probably tissue bound. Hence, digoxin is not effectively removed from body by dialysis.
- Concentration of digoxin in the heart is 30 times than that in the plasma.

- Half-life of digoxin is 1.6 days, and the effects may persist for 24–36 hours after the last dose.
- 85% of digoxin is excreted by the kidneys, and the remaining 15% in the stool through biliary excretion.

Indications

- Cardiac arrhythmias, particularly supraventricular tachycardia, and atrial fibrillation with a fast ventricular rate.
- Severe heart failure in sinus rhythm; most effective in those with impaired ventricular contractility. It has an impact on symptoms and hospitalisation rates but not on mortality in patients with CHF.
- Heart failure accompanied by atrial fibrillation or flutter with a rapid ventricular rate (often used in combination with β-blockers or calcium channel blockers).

Dosage and Route of Administration

- Digoxin loading is done by giving 0.25–0.5 mg orally or intravenously initially, followed by 0.25 mg 6 hourly to a total dose of 1–1.5 mg.
- Maintenance therapy is by a daily oral dose of 0.125–0.375 mg (½–1½ tablets). Maintenance dose should be reduced in those with renal impairment.

Digoxin Toxicity and Its Management

Cardiac manifestations	Extracardiac manifestations	Management of toxicity
• Bradycardia • Multiple ventricular ectopics • Ventricular bigeminy • Paroxysmal atrial tachycardia with block • Ventricular tachycardia (VT) • Ventricular fibrillation • Conduction defects	• Anorexia, nausea, vomiting, diarrhoea • Altered colour vision	• Stop digoxin, check urea, electrolytes and plasma digoxin concentration • Correct hypokalaemia and dehydration • Correct bradycardia using atropine or pacing • Treat atrial tachycardia with β-blockers • Treat VT with lignocaine or amiodarone • Antidigoxin antibodies rarely needed

Q. Discuss the role of diuretic therapy in the management of heart failure.

- Diuretics should be used if necessary to achieve euvolaemia in fluid overloaded patients. In patients with systolic left ventricular dysfunction, use of diuretics as monotherapy should be avoided. They should always be combined with an ACE inhibitor to maintain euvolaemia.
- The site of action, dosage, route of administration and individual side effects of the commonly used diuretics is summarised in the information box, given at the end of this discussion.

Relative Potency of Diuretics

- Low potency—Acetazolamide and potassium sparing diuretics
- Medium potency—Thiazides
- High potency—Loop diuretics

Thiazides

- Mechanism of action
  - Inhibit reabsorption of sodium and chloride mainly in the distal tubule and also in the proximal tubule to a lesser degree.
- Side effects
  - Main side effects are hypokalaemia and metabolic alkalosis.
  - Other side effects—hyperuricaemia, hyperglycaemia, hyperlipidaemia, hyponatraemia, hypersensitivity.
- Notes
  - Thiazides are ineffective when the glomerular filtration rate is less than 30 mL/minute.

- Hypokalaemia induced by thiazides is prevented by either oral potassium chloride supplementation or combining with a potassium-sparing diuretic.
- Thiazides are useful in the initial management of chronic heart failure of mild to moderate severity.

Carbonic Anhydrase Inhibitors

- Acetazolamide is the only drug currently used.
- Mechanism of action
  - Inhibits the reabsorption of sodium bicarbonate mainly in the proximal tubule, and to a lesser degree in the distal tubule.
- Side effects
  - For side effects, refer table.
- Note
  - Rarely used at present. May be useful in patients with high serum bicarbonate levels (e.g. cor pulmonale, metabolic alkalosis).

Loop Diuretics

- Mechanism of action
  - Inhibit reabsorption of sodium, chloride and potassium, mainly in the thick ascending limb of loop of Henle and to a lesser degree in the proximal tubule.
  - Increase renal blood flow by cortical vasodilatation.
- Side effects
  - Main side effects are hypokalaemia and metabolic alkalosis.
  - Other side effects are postural hypotension, hypomagnesaemia, hyperuricaemia, hyperglycaemia and hypersensitivity.
- Notes
  - Loop diuretics are of particular value in three situations:
    - Acute pulmonary oedema
    - Severe refractory heart failure
    - When renal function is impaired
  - All non-steroidal anti-inflammatory drugs, including aspirin, blunt the response of loop diuretics.
  - Hypokalaemia induced by loop diuretics is prevented by oral potassium chloride supplementation or combining it with a potassium-sparing diuretic.
  - In acute CHF or worsening of chronic heart failure, intravenous loop diuretics are often used. When compared with intermittent bolus dosing, a loading dose followed by continuous infusion has been shown to have a larger diuretic and natriuretic effect.
  - Torasemide has been shown to have a greater bioavailability and more consistent rate of absorption in patients with heart failure than furosemide or bumetanide.

Potassium Sparing Diuretics

- Mechanism of action
  - Spironolactone and eplerenone are aldosterone antagonists and act on the distal tubule and collecting duct by competitive inhibition of aldosterone.
  - Amiloride and triamterene block sodium reabsorption and secondarily inhibit potassium secretion in the distal tubules.
- Side effects
  - For individual side effects of the three drugs, refer table.
- Notes
  - Therapeutic efficacy of potassium-sparing diuretics is low when used alone. They are more effective in combination with thiazides or loop diuretics.
  - Potassium-sparing diuretics should not be administered alone to patients with hyperkalaemia, renal failure or hyponatraemia.

Diuretics—Summary

● A brief account of the site of action, dose and side effects of the commonly used diuretics is given below in the information box. The side effects given in the information box are those of the individual drugs.

Group/name	Site of action	Dose/day, route	Individual side effects
● **Thiazides**			
● Chlorothiazide	Distal tubule	250–1000 mg PO, IV	Electrolyte disturbances
● Hydrochlorothiazide	Distal tubule	25–100 mg PO	Electrolyte disturbances
● Chlorthalidone	Distal tubule	25–100 mg PO	
● Indapamide	Distal tubule	2.5–5 mg PO	
● Metolazone	Proximal and distal tubules	2.5–20 mg PO	Hyperuricaemia, glucose intolerance
● **Carbonic anhydrase inhibitors**			
● Acetazolamide	Proximal tubule	250–500 mg PO	Hypokalaemia, acidosis, hypersensitivity
● **Loop diuretics**			
● Furosemide	Loop of Henle	20–60 mg PO, IV, IM	Ototoxicity
● Bumetanide	Loop of Henle	0.5–2 mg PO, IV, IM	Myalgia
● Ethacrynic acid	Loop of Henle	25–100 mg PO, IV	Ototoxicity
● Torasemide	Loop of Henle	5–100 mg PO, IV	Acid–base disturbances
● **Potassium sparing diuretics**			
● Spironolactone	Distal tubule and collecting duct	50–200 mg PO	Gynaecomastia, hyperkalaemia, acidosis
● Triamterene	Distal tubule and collecting duct	100–200 mg PO	Hyperkalaemia, acidosis, renal stones
● Amiloride	Distal tubule and collecting duct	5–10 mg PO	Hyperkalaemia, acidosis

Choice of Diuretic

● Combined use of diuretics is indicated for three reasons:
  ● To avoid electrolyte disturbances that occur with the isolated use of a powerful agent like a loop diuretic
  ● For increasing salt and water excretion in refractory oedema
  ● To avoid the ototoxicity from large doses of loop diuretics
● Oral thiazides are useful for chronic cardiac oedema of mild to moderate degree.
● A loop diuretic given alone or in combination with a potassium sparing diuretic is the agent of choice in severe heart failure refractory to other diuretics.
● A combination of a loop diuretic plus a thiazide plus a potassium-sparing diuretic is used in very severe heart failure.
● In severe heart failure, metolazone may be added with frequent measurement of creatinine and electrolytes.
● In patients who are unable to tolerate even low doses of spironolactone due to hyperkalaemia and renal dysfunction, amiloride or triamterene may be used.
● Diuretics should never be used alone to treat heart failure because they do not prevent the progression of disease or maintain clinical stability over time.

Spironolactone and Eplerenone (Aldosterone Antagonists)

● These are very effective in patients with heart failure and severe secondary hyperaldosteronism. Randomised trials have shown that aldosterone antagonism with spironolactone or eplerenone lowers mortality and morbidity in patients with systolic dysfunction who have class III or IV symptoms despite use of other drugs and ejection fraction ≤35%. Since hyperkalaemia is a common adverse effect, spironolactone or eplerenone may be combined with other diuretics. The combination of ACE inhibitors, angiotensin-receptor blockers and spironolactone (or eplerenone) should be avoided because of a significantly increased risk for hyperkalaemia.

Q. Discuss the role of vasodilator therapy in heart failure.

Q. Briefly explain about afterload reduction therapy.

- Heart failure is associated with:
  - Increase in left ventricular afterload from peripheral vasoconstriction.
  - Increase in preload from an elevated ventricular end-diastolic volume.
- Vasodilator therapy in heart failure is designed to reduce the preload or afterload or both of a failing ventricle. This is accomplished by relaxation of vascular smooth muscle in the periphery (vasodilatation).
- Vasodilators should not be used in patients with hypotension.

Classification

Venous Dilators

- Act by relaxing the vascular smooth muscle of the systemic venous bed.
- They reduce the preload by pooling of blood in the venous bed and hence reducing the venous return, which results in a reduction in ventricular end-diastolic volume.

Arteriolar Dilators

- Act by relaxing the vascular smooth muscle of the arterial bed.
- They reduce the left ventricular afterload and hence increase the stroke volume.

Balanced Vasodilators

- Act by a generalised relaxing effect on the vascular smooth muscle of both venous and arterial beds.
- They reduce both preload and afterload.

Vasodilators Used in the Treatment of Heart Failure

- ACE inhibitors are the drugs of choice in the treatment of heart failure and are superior to other vasodilators.
- If the patient cannot tolerate ACE inhibitors or has contraindications to their use, other vasodilators may be used. One of the recommended combinations is the use of hydralazine and long-acting nitrates. This combination improves clinical outcome and decreases mortality in patients with heart failure and depressed ejection fraction.
- Nesiritide (synthetic form of BNP) is useful in acute left ventricular failure. Besides its vasodilatory effect it also attenuates neurohormonal activity. It decreases sympathetic tone as well as inhibits production of renin, aldosterone and endothelin. Additionally, it promotes natriuresis and diuresis at the level of the kidney while maintaining glomerular filtration rate and renal blood flow. A concern with its use is a possibility of worsening of renal function, particularly in patients with systolic blood pressure <90 mmHg.

Venous dilators (preload reduction)	Arteriolar dilators (afterload reduction)	Balanced dilators (preload and afterload reduction)

• Nitroglycerine
  • 10–200 μg/minute IV
  • 0.5–1 inch TID TD
  • 0.3–0.6 mg/dose SL
• Isosorbide dinitrate
  • 10–60 mg TID PO
	• Hydralazine
	  • 25–100 mg TID PO
	• Minoxidil
	  • 2.5–10 mg TID PO
		• Sodium nitroprusside
		  • 10–300 μg/minute IV
		• Prazosin
		  • 1–10 mg TID PO
		• Captopril
		  • 6.25–25 mg TID PO
		• Enalapril
		  • 5–10 mg BD PO
		• Lisinopril
		  • 10–20 mg daily PO

TD—Transdermal. SL—Sublingual. PO—Per oral.		

Q. What is the role of angiotensin-converting enzyme inhibitors in the management of heart failure?

Q. Explain the role of ACE inhibitors in hypertension.

- ACE inhibitor therapy should be considered a priority in all patients with CHF.
- Asymptomatic patients with a documented left ventricular systolic dysfunction should also be treated with an ACE inhibitor to delay or prevent the development of heart failure. ACE inhibitors also reduce the risk of myocardial infarction and sudden death in this setting.

- For a proper understanding of the ACE inhibitors one should be familiar with the renin–angiotensin–aldosterone system. The renin–angiotensin–aldosterone system is summarised in the flow diagram (given below).
- ACE inhibitors inhibit the conversion of angiotensin I to angiotensin II. Hence the ACE inhibitors counteract the actions of angiotensin II.
- They act in heart failure by:
  - The vasodilator effect that will reduce preload and afterload and so improves cardiac function.
  - Diuresis with elimination of sodium and water. Plasma potassium levels are preserved.
  - An important effect of ACE inhibitors is to reduce the cardiac remodelling that otherwise has a deleterious effect and is responsible for progression of congestive failure, particularly in patients with ischaemic heart disease.
- They act in hypertension by:
  - Inhibiting the generation of angiotensin II that is a potent vasoconstrictor.
  - Inhibiting the degradation of bradykinin that is a potent vasodilator.
  - Altering prostaglandin production.
  - Blocking the angiotensin-mediated increase in sympathetic activity.

Renin–Angiotensin–Aldosterone System
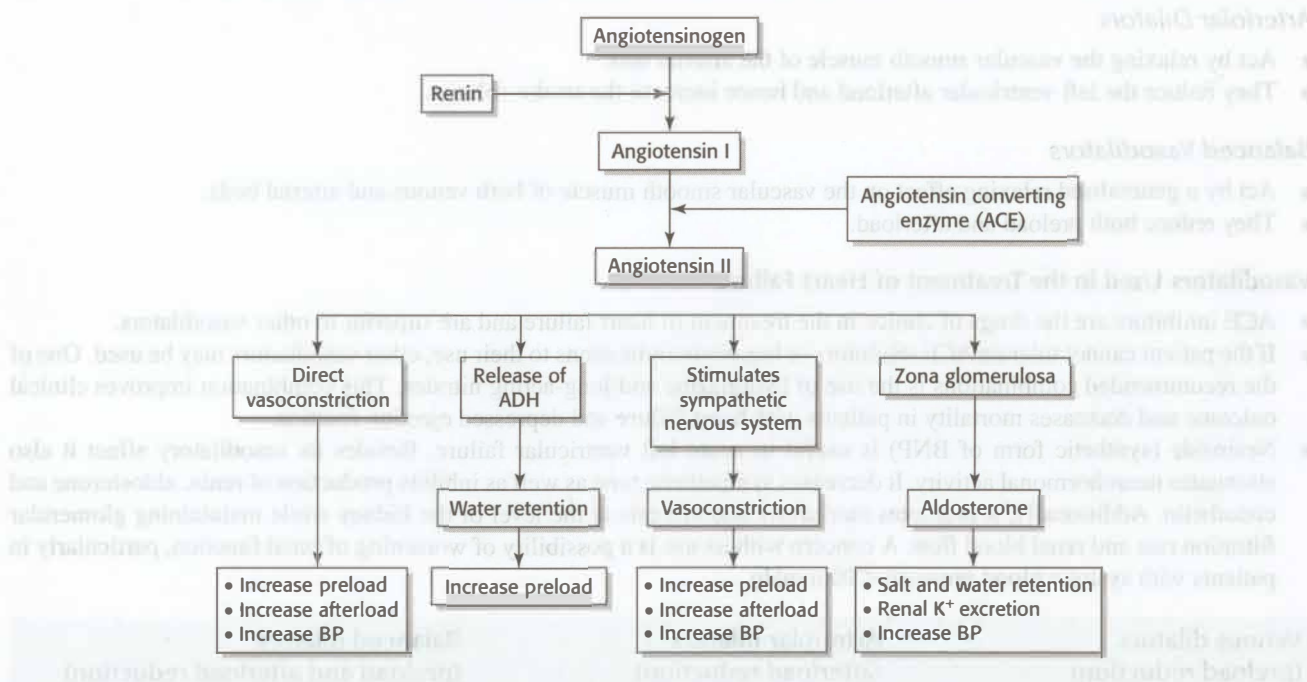
Precautions with ACE Inhibitors

- Can cause profound hypotension with postural symptoms.
- Can cause deterioration in renal function, especially in patients with bilateral renal artery stenosis or pre-existing renal disease. So, renal functions should be monitored.
- Severe hypotension can occur with the first dose, especially if given in the presence of hypovolaemia or hyponatraemia.
- Withhold diuretics for at least 24 hours before the initiation of therapy.
- Start the drug only with a small dose (e.g. 6.25 mg of captopril) while the patient is supine and under observation.
- Risk of hyperkalaemia with simultaneous administration of potassium supplements or potassium-sparing diuretics should be kept in mind.

Commonly Used ACE Inhibitors

Drug	Initial dose	Target dose
Captopril	6.25 mg TID	12.5–50 mg TID
Enalapril	2.5 mg/day	10 mg BID
Lisinopril	2.5 mg/day	20 mg/day
Ramipril	1.25 mg/day	5 mg BID
Perindopril	2 mg/day	8–16 mg OD

Note: Every effort should be made to up-titrate to the highest tolerated dose of ACE inhibitor. The end point for blood pressure can be as low as 90 mmHg systolic blood pressure as long as the patient is asymptomatic. If this is not possible a lower dose is preferable to none at all.

Indications

- Mild to severe forms of heart failure, particularly with systolic dysfunction.
- Hypertension (particularly with high plasma renin activity), renal or renovascular hypertension, accelerated hypertension and malignant hypertension.

Note: Angiotensin-receptor antagonists (e.g. candesartan, valsartan, losartan, etc.) may be used as an alternative to ACE inhibitors for patients who are ACE intolerant. They may also be used in conjunction with ACE inhibitors in patients with heart failure who remain symptomatic and in whom an aldosterone antagonist is not indicated or tolerated; however, this may increase adverse effects, particularly deterioration in renal functions and hyperkalaemia. Routine combined use of an ACE inhibitor, ARB, and aldosterone antagonist is potentially harmful.

Contraindications

- Bilateral renal artery stenosis
- Artery stenosis of a single functioning kidney
- Pregnancy
- Hyperkalaemia

Side Effects

- Common—Dry cough.
- Less common—Hypotension, hyperkalaemia, deterioration in renal function, angioedema, skin rash, altered taste, and leucopenia.

Q. What is the role of β-blockers in the management of congestive heart failure?

- For proper understanding of the role of β-blockers in patients with CHF, one should be familiar with the role of sympathetic system in the pathogenesis of CHF (see renin–angiotensin–aldosterone system).
- β-blocker therapy is indicated in all patients with systolic heart failure who remain symptomatic despite appropriate doses of ACE inhibitors, except those with dyspnoea at rest, those who are volume overloaded, those who are haemodynamically unstable or those with contraindications to their use (bradycardia, bronchospasm, heart block). Those with asymptomatic systolic failure also benefit from the use of these agents.
- Commonly used β-blockers include carvedilol, metoprolol (long acting) and bisoprolol.
- The starting dose should be low which is doubled every 3–4 weeks until the patient is unable to tolerate it (due to bradycardia, hypotension or side effects) or the target dose is reached.

Drug	Initial dose	Target dose
• Carvedilol	3.125 mg/day	12.5–25 mg/day
• Bisoprolol	1.25 mg/day	10 mg/day
• Metoprolol	25 mg/day	100–200 mg/day

Q. What are the newer therapeutic options in patients with congestive heart failure?

- Brain-type natriuretic peptide (BNP)
- Endothelin antagonists
- Neutral endopeptidase inhibitors
- Arginine vasopressin antagonists
- TNF-inhibitors
- Erythropoietin
- Cardiac assist devices

Q. Define cor pulmonale. What are the types of cor pulmonale?

- Cor pulmonale is the dilatation with or without hypertrophy of right ventricle due to an increase in its afterload, which results from diseases of lung, pulmonary circulation or thorax, but without left-sided heart disease. The right heart dysfunction results from pulmonary hypertension.

- The presence of overt right heart failure is not essential to make the diagnosis of cor pulmonale, but right heart failure is a common consequence.
- Pulmonary hypertension in cor pulmonale is defined as pulmonary arterial pressure above 25 mmHg with a pulmonary capillary wedge pressure, left atrial pressure or left ventricular end-diastolic pressure of less than 15 mmHg.

Types

- Acute cor pulmonale
- Chronic cor pulmonale
  - Acute cor pulmonale occurs following a massive pulmonary embolism with acute pulmonary hypertension, resulting in right ventricular dilatation and failure, but no hypertrophy.
  - Chronic cor pulmonale is defined as a combination of hypertrophy and dilatation of the right ventricle secondary to pulmonary hypertension that results from diseases of lung, pulmonary circulation or thorax.

Q. What is acute cor pulmonale? Discuss the clinical manifestations of acute cor pulmonale.

- Acute cor pulmonale usually follows acute massive pulmonary embolism that is sufficient enough to obstruct more than 60% of pulmonary circulation. It leads to acute pulmonary hypertension, acute right ventricular dilatation and failure.

Clinical Features

• Signs of deep venous thrombosis	• Signs of acute right ventricular failure
• Acute dyspnoea, haemoptysis	• Raised jugular venous pressure
• Syncope or cardiac arrest	• Parasternal heave
• Tachypnoea, tachycardia, hypotension	• Right ventricular third heart sound and gallop
• Chest pain	

Q. Discuss the aetiology, pathogenesis, clinical features, investigations and management of chronic cor pulmonale.

- Chronic cor pulmonale is defined as a combination of hypertrophy and dilatation of the right ventricle secondary to pulmonary hypertension, which results from diseases of lung, pulmonary circulation or thorax.

Aetiology

Diseases of lung	Diseases of pulmonary circulation
• Chronic obstructive pulmonary disease (COPD) (chronic bronchitis and emphysema)	• Recurrent pulmonary thromboembolism
• Chronic bronchial asthma	• Primary pulmonary hypertension
• Pulmonary tuberculosis	• Collagen vascular diseases
• Interstitial lung disease	• Chronic liver disease
• Diffuse bronchiectasis	**Diseases of thorax**
• High altitude dwelling	• Kyphoscoliosis
• Cystic fibrosis	• Neuromuscular diseases
• Pleural fibrosis	• Sleep apnoea syndrome
	• Obesity

- Chronic obstructive pulmonary disease (COPD—including chronic bronchitis and emphysema) causes more than 50% cases of chronic cor pulmonale.
  - Patients with chronic bronchitis develop erythrocytosis, oedema and early onset of cor pulmonale (blue bloaters).
  - Patients with emphysema develop cor pulmonale later (pink puffers).
  - Chronic bronchial asthma rarely leads to chronic cor pulmonale.

Pathogenesis

- Increased pulmonary vascular resistance and pulmonary hypertension are the central mechanisms in all cases of chronic cor pulmonale.

- Hypoxaemia not only promotes vasoconstriction but also contributes to the process of vascular remodeling by stimulating smooth muscle proliferation.
- Other possible mechanisms include action of inflammatory mediators on pulmonary vasculature and endothelial dysfunction (disturbance in balanced release of mediators with vasodilatory properties such as nitric oxide or prostacyclin, and mediators with vasoconstrictive properties such as endothelin-1 or angiotensin).

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                      ┌──────────────────┐
    ┌──────────┐      │ Chronic lung disease,│      ┌──────────────┐
    │ Hypoxia  │◄─────│    e.g. COPD     │─────►│ Acidosis and │
    └──────────┘      └──────────────────┘      │ hypercapnia  │
                                │                └──────────────┘
                                ▼
                      ┌──────────────────┐
                      │ Reduction in pulmonary │
                      │   vascular bed   │
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    │ Polycythaemia and│──►┌──────────────────┐
    │  hyperviscosity  │   │ Pulmonary hypertension │◄──
    └──────────────────┘   └──────────────────┘
                                │
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                      │ Hypertrophy and dilatation │
                      │  of the right ventricle │
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                      │ Right ventricular failure │
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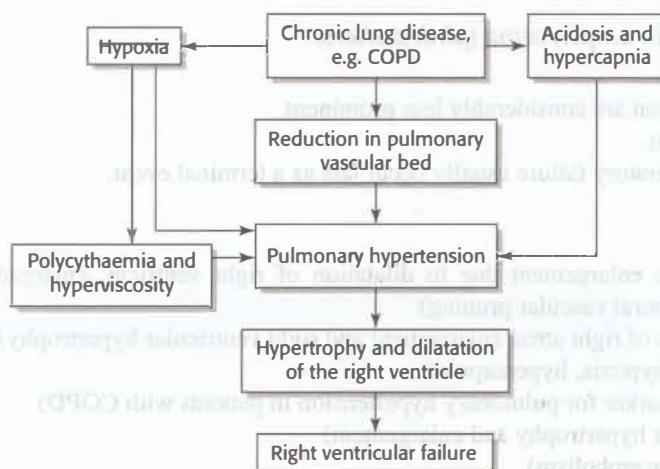
Clinical Features

Symptoms

- There is no symptom that is specific for chronic cor pulmonale. There is overlap between symptoms of cor pulmonale and those due to underlying COPD.
  - Dyspnoea not relieved by sitting up, due to pulmonary hypertension
  - Dry cough
  - Fatigue
  - Atypical anterior chest pain due to dilatation of the root of pulmonary artery
  - Exercise-induced peripheral cyanosis and excessive daytime somnolence

Signs

- Tachypnoea, even on mild exertion
- Ankle oedema
- Prominent *a* waves on JVP
- Right ventricular heave in the left parasternal region and epigastrium
- Loud pulmonary component (P_2) of second heart sound, often palpable
- Right-sided fourth heart sound
- Pulmonary ejection sound
- Ejection systolic murmur at pulmonary area
- Pansystolic murmur of tricuspid regurgitation (with very high pulmonary arterial pressure)
- Early-diastolic murmur of pulmonary regurgitation (with very high pulmonary arterial pressure)

Overt Right Heart Failure

- Overt right heart failure in a patient with chronic cor pulmonale is suggested by the following signs:
  - Increasing peripheral oedema
  - Raised jugular venous pressure and positive hepatojugular reflux
  - Tender hepatomegaly
  - Cardiac enlargement
  - Right ventricular third heart sound and a gallop rhythm
  - Right sided fourth heart sound
- However, symptoms and signs of right heart failure as peripheral oedema, distended jugular veins and palpable liver can be observed in patients with COPD and cor pulmonale without right heart failure.

Additional Clinical Features in Chronic Bronchitis (Blue Bloaters)

- Chronic cough with sputum production
- Frequent mucopurulent exacerbations
- Secondary erythrocytosis
- Repeated episodes of right heart failure and respiratory failure

Additional clinical features in emphysema (pink puffers)

- Severe exertional dyspnoea.
- Cough and sputum production are considerably less prominent.
- Erythrocytosis is uncommon.
- Right heart failure and respiratory failure usually occur late as a terminal event.

Investigations

- Chest radiography (cardiac enlargement due to dilatation of right ventricle; enlarged main and hilar pulmonary arterial shadows with peripheral vascular pruning)
- Electrocardiogram (features of right atrial enlargement and right ventricular hypertrophy)
- Arterial blood gas studies (hypoxia, hypercapnia)
- BNP (may be a useful biomarker for pulmonary hypertension in patients with COPD)
- Echocardiography (chamber hypertrophy and enlargement)
- Nuclear scan (for pulmonary embolism)
- Right heart catheterisation (rarely required)

Management of Chronic Cor Pulmonale

- General measures
- Additional measures in COPD-induced cor pulmonale
- Surgical treatment

General Measures

- Treatment to decrease pulmonary hypertension
- Treatment of right heart failure

Treatment to Decrease Pulmonary Hypertension

- Treatment of underlying disease
- Oxygen therapy is the most important treatment in reducing pulmonary hypertension. In fact, long-term oxygen therapy is the only treatment shown to retard the progression of pulmonary hypertension.
  - Chronic oxygen therapy is initiated if the arterial oxygen tension is 55 mmHg or less.
  - Oxygen should be administered in a controlled manner. The inspired oxygen concentration is adjusted to produce PaO_2 of 60 mmHg or more.
  - Oxygen should be administered for a minimum period of 12–15 hours/day.

Treatment of Right Heart Failure

- Salt restriction
- Digoxin (role is controversial)
- Diuretics
- Phlebotomy when haematocrit is more than 60%
- Vasodilator therapy to reduce afterload with hydralazine and nifedipine appears to be beneficial. These are however not recommended because of their potential detrimental effects on gas exchange produced by inhibition of hypoxic pulmonary vasoconstriction and their lack of effectiveness after long-term treatment.
- Prostacycline (epoprostenol and prostaglandin I_2) therapy has not been studied systematically in cor pulmonale secondary to lung diseases.
- Sildenafil, a phosphodiesterase-4 inhibitor, has also been used in the treatment of pulmonary hypertension with variable results.
- Bosentan, an endothelin-1 receptor blocker, has some role in idiopathic pulmonary hypertension.

Additional Measures in COPD-Induced Cor Pulmonale

- Avoidance of airway irritants like tobacco smoke.
- Bronchial toilet for removal of secretions.
- Treatment of respiratory infections with antibiotics.
- Bronchodilators are useful.
- Corticosteroids may be beneficial in patients with bronchospasm.
- Tranquillisers, sedatives and narcotics are preferably avoided.

Surgical Treatment

- Pulmonary embolectomy in unresolved pulmonary emboli
- Heart-lung transplantation in patients with primary pulmonary hypertension
- Unilateral lung transplantation in patients with interstitial lung disease

Q. Define rheumatic fever. Discuss the aetiology, pathogenesis, clinical features, investigations and management of rheumatic fever. Add a note on rheumatic fever prophylaxis.

Definition

- Rheumatic fever is an inflammatory disease occurring as a delayed sequel to pharyngeal infection with group A streptococci. It primarily involves the heart, joints, central nervous system, skin and subcutaneous tissues.

Aetiology

- Rheumatic fever follows an antecedent pharyngeal infection with group A β-haemolytic streptococcus. The latent period between the pharyngeal infection and the onset of rheumatic fever ranges from 1 to 5 weeks, the average duration being 19 days.
- Cutaneous streptococcal infection that commonly causes acute post-streptococcal glomerulonephritis has not been shown to cause rheumatic fever.
- The various serotypes of group A streptococci vary in their rheumatogenic potential. M-protein is one of the best-defined determinants of bacterial virulence. The highly prevalent M-type 12 usually does not produce rheumatic fever. M-type 5 commonly causes rheumatic fever. The other rheumatogenic serotypes include 1, 3, 6, 14, 18, 19 and 24.
- Fewer than 2–3% of previously healthy persons develop rheumatic fever following group A β-haemolytic streptococcal pharyngitis.

Pathogenesis

- Precise pathogenetic mechanisms of rheumatic fever have not been defined.

Molecular Mimicry

- Streptococcus-induced autoimmunity is believed to be the mechanism resulting in rheumatic process. Several streptococcal antigens have demonstrated cross-reactivity with cardiac and other tissues ("molecular mimicry").

Streptococcal Superantigens

- Superantigens are a unique group of glycoproteins synthesised by bacteria and viruses that can bridge class II major histocompatibility complex molecules to specific T-cell receptors, stimulating antigen binding. The T-cells are activated to release cytokines or become cytotoxic, and these can become autoreactive.
- Some of the superantigens on streptococci include M-protein fragments and pyrogenic exotoxin that may have role in the pathogenesis of rheumatic fever.
- Superantigens may also stimulate B-lymphocytes. Streptococcal erythrogenic toxin may behave like a superantigen for B-cell, leading to production of autoreactive antibodies.

Host Factors

- There is strong evidence that an autoimmune response to streptococcal antigens mediates the development of rheumatic fever only in a susceptible host (only 0.3–3% of individuals with acute streptococcal pharyngitis go on to develop rheumatic fever).
- In India, HLA-DR3 is present more frequently in rheumatic fever patients. Also, Indians with rheumatic fever have low frequency of HLA-DR2.

Epidemiology

- Rheumatic fever is a worldwide disease. It is a major cause of death and disability in children and adolescents in socio-economically deprived areas.
- It is most prevalent in areas of poor economic conditions, overcrowding and substandard housing. All of these factors in general reflect the frequency and severity of streptococcal pharyngitis.
- It is common to see multiple cases among the siblings and others in the same family.
- In India, the annual incidence of rheumatic fever has been estimated to be between 0.18 and 0.3 per 1000 school-children.
- The peak incidence is between 5 and 15 years. It is relatively rare in infants and young children below the age of 5 years.
- No clear-cut sex predilection exists though certain clinical manifestations, such as mitral stenosis and Sydenham chorea have a female preponderance after puberty.

Pathology

- Acute rheumatic fever is characterised by exudative and proliferative inflammatory lesions of the connective tissues. It mainly involves the heart, joints and subcutaneous tissues.

Heart

- In the heart, all three layers (endocardium, myocardium and pericardium) are involved resulting in rheumatic pancarditis.
- Myocardium
  - Myocardium shows the pathognomonic myocardial Aschoff body. Aschoff bodies are small granulomas with a central zone of fibrinoid degeneration surrounded by lymphocytes, plasma cells and large basophilic cells (Aschoff giant cells) and fibroblasts.
  - Aschoff bodies may persist for many years in chronic rheumatic inflammation, especially in those who develop severe mitral stenosis.
  - Eventually, the Aschoff body is converted into a spindle-shaped or triangular scar.
- Endocardium
  - Rheumatic endocarditis produces verrucous valvulitis. It may later lead to healing with fibrous thickening and adhesions of valve commissures, leaflets and chordae tendineae. End result of this is varying degrees of stenosis and regurgitation of valves.
  - Mitral valve is the most commonly involved, aortic valve next, tricuspid valve rarely and pulmonary valve almost never.
- Pericardium
  - Pericarditis produces pericardial effusion and a thick serous exudate that gives the "bread and butter" appearance macroscopically.

Extracardiac Lesions

- Joint involvement with an effusion, later healing without any residual deformity
- Subcutaneous nodules showing many histological features similar to that of Aschoff body
- Pleural lesions (fibrinous pleurisy)
- Pulmonary lesions (rheumatic pneumonitis)
- Non-specific findings in the brain of patients with chorea

Clinical Manifestations

Sore Throat

- Only two-thirds of patients remember having any upper respiratory symptoms in the past 1–5 weeks.

Polyarthritis

- Arthritis is the most common major manifestation of rheumatic fever and is present in nearly 75% of cases.
- Classical presentation is acute migratory polyarthritis with features of a febrile illness.
- Most commonly involved joints are large joints of the extremities.
- Hips and small joints of hands and feet are affected occasionally.
- Involvement of spine, sternoclavicular and temporomandibular joints is rare.
- Affected joints show signs of inflammation with or without effusion.

- "Migratory involvement" or "flitting" nature is characteristic. As pain and swelling subside in one joint, others tend to get involved.
- Over a period of time involved joints heal without any residual deformity. Jaccoud's arthritis is a rare deformity of the metacarpophalangeal joints following repeated attacks of rheumatic fever.
- To be acceptable as a major criterion for diagnosis:
  - Polyarthritis should involve two or more joints.
  - Should be associated with at least two minor manifestations
  - Should be associated with a high titre of one of the streptococcal antibodies

Post-Streptococcal Reactive Arthritis (PSRA)

- Development of arthritis after an episode of Group A streptococcal pharyngitis without other major criteria of acute rheumatic fever
- Occurs ~ 10 days after pharyngitis and does not respond readily to acetylsalicylic acid. Arthritis of rheumatic fever occurs 14 to 21 days after an episode of Group A streptococcal pharyngitis and responds rapidly to acetylsalicylic acid.
- Arthritis of PSRA is cumulative and persistent, and can involve large joints, small joints or axial skeleton. On the other hand, arthritis of rheumatic fever is migratory and transient, and usually involves only the large joints.
- A small proportion of patients with PSRA may subsequently develop valvular heart disease; therefore, patients should be observed carefully for several months for evidence of carditis.

Carditis

- Features of carditis develop early (within 3 weeks of onset) and occur in 40–50% of cases.
- It is more common in younger children, and may be asymptomatic and picked up on echocardiography only.
- Rheumatic fever may involve endocardium, myocardium and pericardium resulting in pancarditis.
- Involvement of myocardium alone without pericardial and endocardial involvement does not constitute major criterion.
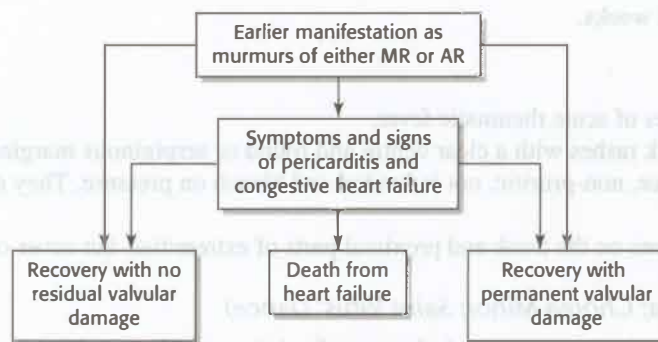
Usual sequence of events in carditis

Manifestations of Carditis

- Myocarditis
  - Tachycardia disproportionate to fever and persisting in sleep
  - Dropped beats
  - Third heart sound (S_3), fourth heart sound (S_4) or a summation gallop
  - Foetal or "tic-tac" quality of heart sounds
  - Arrhythmias, of which prolongation of PR interval being the commonest
  - Features of congestive heart failure
- Endocarditis
  - Apical systolic murmur of mitral regurgitation
  - Apical mid-diastolic murmur (Carey–Coombs murmur) due to nodules on the mitral valve leaflets
  - Basal early-diastolic murmur of aortic regurgitation
  - In an individual with previous RHD:
    - A definite change in character of murmurs
    - Appearance of a new significant murmur

- Pericarditis
  - Pericardial pain
  - Pericardial friction rub
  - Pericardial effusion (uncommon and always small)

Cardinal Features of Acute Rheumatic Carditis

• Murmurs	• Pericarditis
• Apical systolic murmur	• Cardiomegaly
• Apical mid-diastolic murmur (Carey–Coombs murmur)	• Congestive heart failure
• Basal diastolic murmur	

Diagnosis of Carditis

- Requires the presence of one or more of the following:
  - Appearance of or change in the character of organic murmurs
  - Cardiomegaly
  - Pericarditis or pericardial effusion
  - Congestive heart failure

Subcutaneous Nodules

- Subcutaneous nodules are usually associated with severe carditis and tend to occur several weeks after its onset.
- Description—Small, pea-sized, painless nodules over bony prominences.
- Common sites—Extensor tendons of hands and feet, elbows, margins of patellae, scalp, occiput, over scapulae and over spinous processes of vertebrae.
- Easily missed as skin over them is not inflamed.
- They usually persist for 1–2 weeks.

Erythema Marginatum

- It occurs in nearly 10% cases of acute rheumatic fever.
- These are erythematous pink rashes with a clear centre and round or serpiginous margins. These rashes are transient, migrating from place to place, non-pruritic, not indurated and blanch on pressure. They are brought on by application of heat.
- They are most commonly seen on the trunk and proximal parts of extremities, but never on face.

Chorea (Sydenham's Chorea; Chorea Minor; Saint Vitus' Dance)

- For a detailed description and management of chorea, refer later and also to chapter on "Diseases of the Nervous System".
- Chorea usually appears after a long latent period (up to 6 months) after the initial streptococcal infection.
- It occurs in nearly 15% of first attacks of acute rheumatic fever and is most common between the ages of 7 and 14 years. It is rare after puberty.
- Chorea is characterised by sudden, aimless, irregular movements associated with muscle weakness, emotional instability, obsessions and compulsions, tics and psychotic features.
- Pure chorea is the term used when no previous rheumatic manifestations are noted.

Other Clinical Manifestations of Rheumatic Fever

- Other clinical manifestations include fever, arthralgia, abdominal pain and epistaxis.

Duration of Attack

- The average duration of an untreated attack of acute rheumatic fever is approximately 3 months.
- Chronic rheumatic fever, generally defined as disease persisting for longer than 6 months, occurs in less than 5% of cases and is a cause of persisting congestive heart failure.

Laboratory Features

Isolation of Group A Streptococci

- Group A streptococci may be isolated by throat culture only in a minority of cases. Hence serologic tests are preferred.

Streptococcal Antibody Tests (Serologic Tests)

- These tests confirm a recent streptococcal infection.
- Streptococcal antibody levels are raised in the early stages of acute rheumatic fever. However, their levels may be low or declining in two situations:
  - When the interval between the streptococcal pharyngeal infection and detection of rheumatic fever is more than 2 months (e.g. chorea)
  - In those patients whose only major manifestation is rheumatic carditis
- Common serologic tests done are:
  - Anti-streptolysin O test (ASO)
  - Anti-DNase B
  - Anti-hyaluronidase (AH)
  - Anti-streptozyme test (ASTZ)
- Single titres of ASO more than 250 Todd units in adults and 333 Todd units in children above 5 years are taken as positive. However, a rising titre is even more significant. ASO test is positive in 80% of cases.
- Anti-streptozyme (ASTZ) test is a very sensitive indicator of recent streptococcal infection. Titres more than 200 units/mL are considered positive. The real value of ASTZ test is in ruling out rheumatic fever.
- These four tests when combined together give an accuracy rate of more than 95%.

Acute Phase Reactants

- These tests confirm the presence of an inflammatory process, but are non-specific
  - Erythrocyte sedimentation rate (ESR) is raised.
  - C-reactive protein (CRP) in the blood.
- These two are often normal in chorea.

Other Tests Confirming an Inflammatory Reaction

- Polymorphonuclear leucocytosis
- Increase in serum complements
- Increase in serum mucoproteins, α_2 and γ globulin levels
- Anaemia due to suppression of erythropoiesis

Electrocardiogram

- The most consistent abnormality is a prolongation of the PR interval.
- Less common findings are second degree AV block and some other non-specific changes.

Chest Radiography

- Chest radiography may show evidences of cardiac failure.
  - Cardiomegaly
  - Pulmonary congestion

Echocardiography

- Echocardiography can detect:
  - Myocardial dysfunction
  - Valvular dysfunction
  - Pericardial effusion

Diagnosis of Acute Rheumatic Fever

- For diagnosis, modified T. Duckett–Jones criteria (Revised Jones criteria) or WHO criteria are applied.
- Revised Jones Criteria are for diagnosis of first episode of acute rheumatic fever.

Revised Jones Criteria

Major manifestations	Minor manifestations
• Carditis • Polyarthritis • Chorea • Erythema marginatum • Subcutaneous nodules	• Fever • Arthralgia • Previous rheumatic fever or rheumatic heart disease • Raised ESR • Positive CRP • Prolonged PR interval

- Two major manifestations or one major and two minor manifestations indicate a high probability, with one supporting evidence of preceding streptococcal infection, e.g.
  - Recent scarlet fever
  - Positive throat culture for group A streptococcus
  - Increased streptococcal antibodies
- WHO criteria can be used for both first episode and recurrent episodes of acute rheumatic fever. Supporting evidence of preceding streptococcal infection also includes positive rapid antigen test for group A streptococci on throat swab.

WHO Criteria

- First episode—as per Jones criteria
- Recurrent episode:
  - In a patient without established RHD: as per first episode
  - In a patient with established RHD: requires only two minor manifestations plus evidence of antecedent Group A streptococcus infection as per Jones criteria
- Chorea and indolent carditis do not require evidence of antecedent Group A streptococcus infection or other major criteria

Management of Acute Rheumatic Fever

Bed Rest

- Patients who have not had carditis should be advised bed rest until temperature and ESR are normal.
- Patients who have had carditis should continue to have bed rest for 2–6 weeks after the ESR and temperature have returned to normal.

Antistreptococcal Therapy

- A course of antibiotic should be given to eradicate the streptococci, even if the throat culture is negative. One of the following regimens may be used:
  - Single injection of benzathine penicillin 1.2 million units intramuscularly.
  - Daily injection of procaine penicillin 6,00,000 units intramuscularly for 10 days.
  - Oral erythromycin 20–40 mg/kg/day in three divided doses, in patients who are sensitive to penicillin, or azithromycin in a dose of 500 mg once day for 5 days.

Salicylates

- Aspirin is effective in providing symptomatic relief.
- Aspirin is started at doses of 60 mg/kg/day in six divided doses. Dose is increased gradually until the drug produces either a clinical improvement or systemic toxicity (tinnitus, headache or hyperpnoea). This dose might go up to 120 mg/kg/day or a maximum of 8 g/day.
- Aspirin at this dose should be continued until the ESR is normal, and then gradually tapered over 4–6 weeks.

Corticosteroids

- Indications
  - Patients who have severe carditis manifested by congestive heart failure not responding to aspirin
  - Patients with severe arthritis whose symptoms and signs are not adequately suppressed by aspirin

- Prednisolone is given orally at a dose of 60–120 mg/day in four divided doses until the ESR is normal. It is then gradually tailed off over a period of 2 weeks.
- To prevent a "post-steroid rebound" an "overlap" course of aspirin may be added when the steroid is being tapered off. Aspirin is then continued for an additional 2–3 weeks.
- Monitoring the corticosteroid or aspirin therapy during acute phase as well as while being tapered should be based on indices of healing process:
  - ESR
  - C-reactive protein (CRP)

Supportive Therapy

- Includes treatment of congestive heart failure, valvular lesions, heart blocks and chorea

Prevention of Rheumatic Fever

- Prevention of rheumatic fever includes:
  - "Primary prevention"—prevention of initial rheumatic attacks
  - "Secondary prevention"—prevention of recurrence of rheumatic fever

Primary Prevention

- Primary prevention can be summarised as "accurate diagnosis and treatment of group A streptococcal pharyngeal infection".
- An outbreak of rheumatic fever in a closed population is best treated by mass penicillin prophylaxis.
- Established streptococcal pharyngitis can be treated by procaine penicillin, benzathine penicillin or oral penicillin, or erythromycin or azithromycin.
- In communities where rheumatic fever is endemic, sore throat in children (3–15 years) should be regarded as strepto-coccal infection and be treated as such unless any one of the following clinical characteristics is present: Ulceration, hoarseness, watery nasal secretion or conjunctivitis.

Secondary Prevention (Rheumatic Fever Prophylaxis)

- Rheumatic fever prophylaxis should be given to all patients who have experienced a documented attack of rheumatic fever.
- Duration of prophylaxis is controversial. Broad outlines are:
  - No carditis: For 5 years or until 18 years of age (whichever is longer)
  - Resolved carditis: For 10 years or until 25 years of age (whichever is longer)
  - Severe RHD or if surgery is required: Lifelong or at least till the age of 40 years.
- Decision to continue prophylaxis beyond 5 or 10 years (in first or second group mentioned above) depends on many variables like age of the patient, relative risk of acquiring infection, socio-economic state, etc.
- Regimens: One of the following regimens may be used:
  - Intramuscular injection of 1.2 million units of benzathine penicillin G every 3 weeks (most-efficient regimen)
  - Oral penicillin V 500 mg twice a day
  - Amoxycillin (sustained release) 1 g once a day
  - Sulphadiazine 1 g/day orally as a single dose (in those allergic to penicillins)
  - Erythromycin 250 mg twice a day orally or azithromycin 500 mg once a day (in those allergic to penicillins and sulpha)

Q. Discuss the aetiology, clinical features and management of rheumatic chorea (Sydenham's chorea; Chorea minor; Saint Vitus' dance).

Definition

- Rheumatic chorea is a syndrome characterised by choreic movements, muscle weakness and emotional instability (also refer to chapter on "Diseases of the Nervous System").

Aetiology

- Pharyngeal infection by group A streptococci.
- Chorea is a delayed manifestation of rheumatic fever. Often, there is a long latent period of up to 6 months.
- When no previous rheumatic manifestations are noted, the term pure chorea is used.
- Chorea is more common in females in the age group 5–15 years.

Clinical Features

- Mild forms will appear like increased fidgetiness and may be difficult to diagnose. Following three signs are helpful in mild cases:
  - "Milkmaid's grip"—It is due to inability to maintain muscular contraction. When the patient is asked to squeeze the examiner's fingers, a squeezing and relaxing motion (like milking a cow) occurs, which is described as milkmaid's grip.
  - "Bag-of-worms appearance"—This is asynchronous contractions of the lingual muscles.
  - "Jack-in-the-box sign"—When the patient is asked to keep the tongue protruded out, it retracts involuntarily.
- Well-established cases are easy to diagnose. There are intermittent or continuous, fast, jerky, involuntary movements of the extremities that interfere with normal activity. Movements may be more on one side (hemichorea). Facial chorea results in frequent grimacing, blinking and slurring of speech. These movements subside in sleep and get worsened with emotional disturbances, and during voluntary movements.
- In severe cases the person is unable to get up or sit, and has violent continuous jerks that may cause physical injury.

Additional Features

- Hypotonia
- Pendular knee jerks
- Generalised muscular weakness (mild)
- Emotional instability

Management

- Complete mental and physical rest
- Keep the patient in a quiet room
- Padded side-boards for beds to prevent injury
- Haloperidol or sodium valproate with diazepam
- Rheumatic fever prophylaxis

Q. Discuss the aetiology, pathophysiology, clinical features, investigations and complications of mitral stenosis.

Q. How do you grade the severity of mitral stenosis based on mitral valve orifice size?

Q. Explain briefly about juvenile mitral stenosis and paediatric mitral stenosis.

Anatomy of Normal Mitral Valve

- The mitral valve apparatus is a funnel-shaped structure with its apex in the left ventricle.
- Normal mitral valve orifice is about 4–6 cm^2 (average 5 cm^2).
- The mitral valve apparatus has a mitral annulus and two leaflets namely anterior mitral leaflet (AML) and posterior mitral leaflet (PML). The two leaflets are attached by about 120 chordae tendineae to two papillary muscles.

Altered Anatomy in Rheumatic Mitral Stenosis

Primary Pathological Features

- Thickened mitral cusps with or without calcification
- Fusion of valve commissures (major cause of obstruction)
- Shortening and fusion of chordae tendineae

Secondary Pathological Features

- Left atrial hypertrophy and dilatation
- Left atrial thrombi
- Changes of venous and arterial hypertension in pulmonary vasculature
- Right ventricular hypertrophy

Aetiology of Mitral Stenosis

- Rheumatic fever
- Congenital mitral stenosis
- Coxsackie B virus carditis
- Systemic lupus erythematosus
- Atrial myxoma
- Methysergide treatment

- Malignant carcinoid
- Gout
- Mitral annular calcification
- Mucopolysacchridosis
- Infective endocarditis (extremely rare)
- Rheumatoid arthritis (extremely rare)

- Rheumatic fever is the most common cause of mitral stenosis. But only about one-half of the patients with mitral stenosis will give a history of rheumatic fever or chorea.
- Two-third of all patients with mitral stenosis are females.
- In India, the latent period from the first attack of rheumatic fever to the onset of symptoms of mitral stenosis is much shorter than in the West (where it is average 20 years). This period may be as short as 1–2 years. This is due to repeated attacks of severe carditis in India.
- Juvenile mitral stenosis is common in India. The clinical manifestations occur below the age of 19 years.
- Paediatric mitral stenosis indicates development of clinical manifestations below the age of 12 years.

Severity of Stenosis According to Mitral Valve Size

Severity/stage	Mitral valve orifice
- Minimal	More than 2.5 cm^2
- Mild	1.4–2.5 cm^2
- Moderate	1.0–1.4 cm^2
- Severe (critical, tight)	Less than 1.0 cm^2
	(Normal mitral valve orifice is 4–6 cm^2)

Pathophysiology and Haemodynamics

- In mitral stenosis, the obstruction to the flow of blood from left atrium to left ventricle leads to elevation in left atrial pressure (up to 25 mmHg in severe cases). This rise in left atrial pressure occurs only during exercise in the initial stages, but later it remains elevated even at rest.
- The elevated left atrial pressure is reflected back in the pulmonary veins resulting in pulmonary venous hypertension.
- Subsequently pulmonary arterial hypertension develops. Symptoms and signs of pulmonary venous hypertension abate when pulmonary arterial hypertension sets in.
- Pulmonary arterial hypertension (pulmonary hypertension) results from:
  - "Passive pulmonary hypertension"—passive backward transmission of elevated left atrial pressure.
  - "Reactive pulmonary hypertension"—reflex spasm of pulmonary arterioles in response to elevated pulmonary venous and left atrial pressure.
  - Organic obliterative changes in the pulmonary vascular bed.
- This chronic pulmonary hypertension results in the following consequences:
  - Right ventricular hypertrophy and later dilatation, ultimately resulting in right ventricular failure.
  - Functional tricuspid regurgitation from tricuspid valve ring dilatation secondary to right ventricular dilatation.
  - Pulmonary incompetence (regurgitation) due to pulmonary valve ring dilatation.
- The elevated left atrial pressure results in left atrial dilatation. This enlarged left atrium is prone to:
  - Atrial fibrillation
  - Stasis of blood with thrombus formation
  - Detachment of the thrombus resulting in systemic embolism
- Ejection fraction of left ventricle reduced in approximately one-third of patients due to:
  - Decreased preload from impaired filling
  - Increased afterload secondary to reflex vasoconstriction (secondary to reduced cardiac output)
- Patients with severe mitral stenosis easily decompensate with tachycardia or high flow.
- Atrial contraction helps to maintain flow across the stenotic mitral valve; atrial fibrillation, which is associated with tachycardia, irregular R–R interval and lack of atrial contraction, is often an important precipitating factor for symptoms of dyspnoea.

Pathophysiology
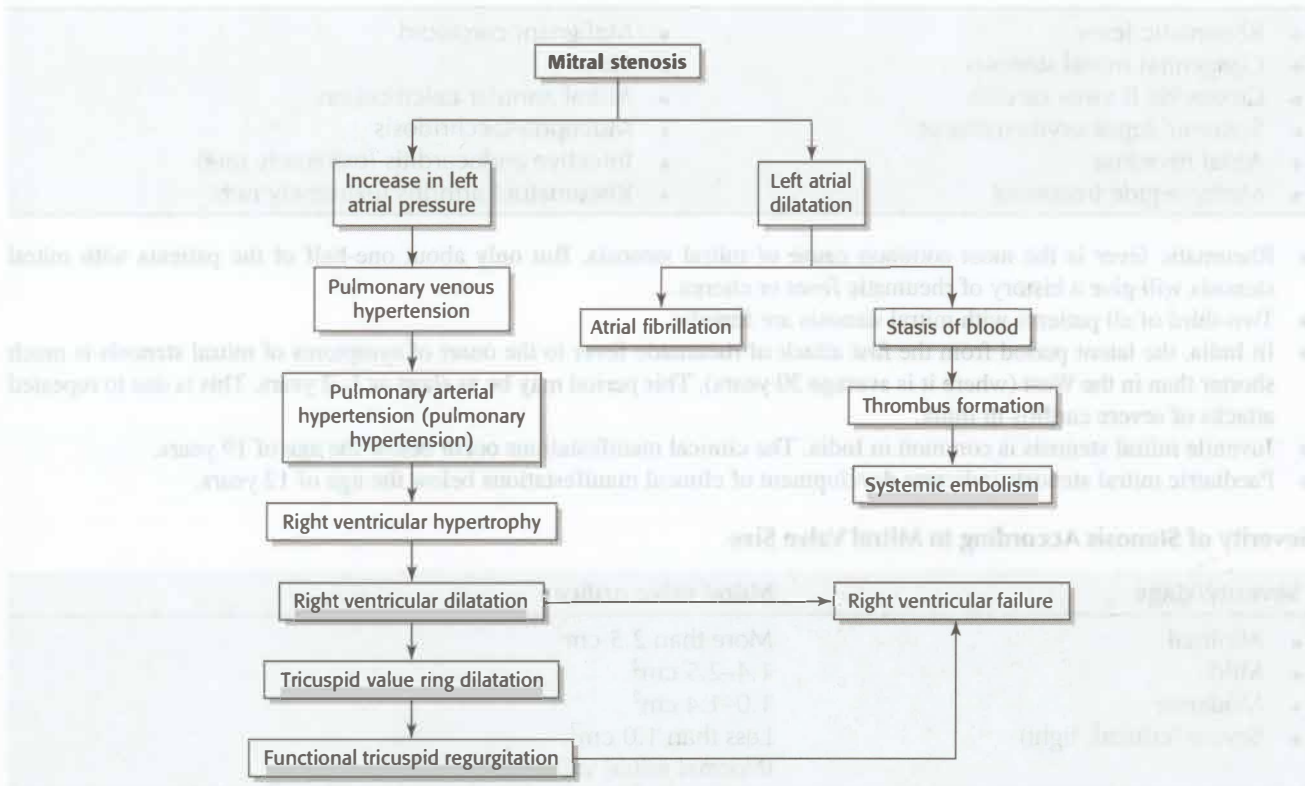
Clinical Features

Symptoms

- Mild-to-moderate mitral stenosis may remain asymptomatic. Lymphatic hyperfunction in such patients may help prevent pulmonary congestion and its attendant symptoms.
- The natural history of mitral stenosis is such that once the patient becomes symptomatic there is gradual and steady deterioration. Persistent inflammatory valve damage and haemodynamic injury contribute to gradual progression. Death occurs in 2–5 years unless the stenosis is corrected.

Dyspnoea

- Dyspnoea is initially exertional, but gradually progresses to a state of breathlessness even at rest.
- Dyspnoea results from pulmonary venous congestion occurring as a result of pulmonary venous hypertension. The fluid is driven out of the pulmonary capillaries into the interstitium, which leads to a decrease in the compliance of the lungs, and consequently increases the work of breathing. This results in dyspnoea.
- Severe exertion, excitement, fever, anaemia, sexual intercourse, pregnancy, thyrotoxicosis and atrial fibrillation can all precipitate or aggravate dyspnoea by elevation of pulmonary capillary pressure.

Orthopnoea and Paroxysmal Nocturnal Dyspnoea

- In the supine position, there is increased venous return to the heart, which will increase pulmonary venous pressure, resulting in orthopnoea and PND.

Pulmonary Oedema

- Pulmonary oedema develops when pulmonary capillary pressure exceeds 25 mmHg, and the resulting transudate cannot be cleared by lymphatics.
- Common precipitating factors of pulmonary oedema are the same as that for dyspnoea (refer above).
- Pulmonary oedema can develop in two forms, either suddenly or gradually, preceded by orthopnoea and PND.

Haemoptysis

- Causes of haemoptysis in mitral stenosis are the following:

  - Rupture of pulmonary–bronchial venous connections secondary to pulmonary venous hypertension
  - Pink frothy sputum of pulmonary oedema
  - Blood-streaked sputum of recurrent bronchitis
  - Pulmonary infarction due to pulmonary embolism

- Haemoptysis subsides as pulmonary arterial hypertension develops.

Winter Bronchitis

- Patients with mitral stenosis are prone to recurrent attacks of bronchitis, particularly in the winter season.

Other Symptoms

- Palpitation.
- Fatigue, loss of appetite and chest pain due to pulmonary hypertension and congestive heart failure.
- Symptoms of right ventricular failure like peripheral oedema, right hypochondrial pain, etc.
- Symptoms related to complications may be present (vide infra).

Physical Signs

General Examination

- Peripheral and facial cyanosis occur in extremely severe cases.
- Mitral facies is seen in severe cases with low cardiac output and peripheral vasoconstriction. The lips and face are cyanotic. Despite this cyanosis there may be a "malar flush" or "florid countenance" (florid appearance) due to dilated veins in the cheek.
- Peripheral oedema in congestive heart failure.

Pulse

- Low volume in severe mitral stenosis
- Irregularly irregular rhythm and varying volume in atrial fibrillation

Blood Pressure

- May be slightly reduced.

Jugular Veins

- Jugular venous pressure is elevated in congestive heart failure.
- Jugular venous pulse.
  - Prominent *a* waves with pulmonary hypertension
  - Absent *a* waves in atrial fibrillation
  - Prominent *v* waves (*c*–*v* waves) and rapid *y* descent in functional tricuspid regurgitation

Inspection and Palpation

- Pre-cordial bulge in long-standing cases with onset of illness early in life
- Apex beat is normal in position in isolated mitral stenosis, whereas it may be shifted with the development of right ventricular hypertrophy.
- Apex beat is tapping in character due to the loud palpable first heart sound.
- Diastolic thrill at the apex, which is best felt with the patient in left lateral position, with breath held in expiration.
- Exercise accentuates the thrill.
- Visible and palpable pulsations in the second left intercostal space from the underlying dilated pulmonary artery in pulmonary hypertension.
- Palpable pulmonary component of the second heart sound (P_2) in the pulmonary area due to pulmonary hypertension.
- Visible and palpable left parasternal heave and epigastric pulsation due to right ventricular hypertrophy.

Auscultation

Loud First Heart Sound

- This is an important finding in mitral stenosis. It is due to closure of the diseased mitral valve with rapid apposition of the leaflets.
- In associated atrial fibrillation the first heart sound varies in intensity.
- A low intensity of the first heart sound in one of the following:

  - Calcification of the mitral valve
  - Dominant associated mitral regurgitation
  - Dominant associated aortic regurgitation

Loud Second Heart Sound

- This is an important sign of pulmonary hypertension.
- The second heart sound is closely split and the pulmonary component of the second heart sound (P_2) is accentuated.

Mitral Opening Snap

- Opening snap (OS) is a sharp, snappy sound occurring in early diastole, following aortic valve closure (A_2).
- It is best heard during expiration, at or just medial to the cardiac apex (sometimes, it is widely heard).
- OS is believed to be caused by an elevated left atrial pressure that sharply forces open the mitral valve during diastole.
- Significance
  - A_2–OS interval signifies severity of mitral stenosis, being close with tighter stenosis. It varies from 0.04 to 0.12 seconds.
  - The OS may become dull (soft) or even absent in severe mitral stenosis if there is calcification or severe fibrosis of the mitral valve. It may also be absent in severe mitral stenosis due to extreme clockwise rotation of heart.
  - Intensities of first heart sound (S_1) and OS correlate with the mobility of the AML (restricted by severe fibrosis or calcification).

Ejection Click

- A pulmonary systolic ejection click may be heard in severe pulmonary hypertension with marked dilatation of pulmonary artery.

Murmur of Mitral Stenosis

- This is a diastolic murmur well localised to the mitral area. It is low pitched, rough and rumbling in character, best heard at the apex with the bell of the stethoscope, with the patient in left lateral position and during expiration. Murmur is accentuated by exercise carried out just before auscultation.
- In early stages of mitral stenosis, the murmur is confined to mid-diastole or pre-systole. Still later, the murmur becomes longer and extends to the first heart sound (S_1), often with a pre-systolic accentuation.
- In patients with sinus rhythm, the murmur is accentuated during atrial systole ("pre-systolic accentuation") as the atrial contraction increases the rate of flow across the stenosed mitral valve.
- The pre-systolic accentuation of the murmur is present:
  - With regular sinus rhythm
  - During long R–R interval in atrial fibrillation
- The pre-systolic accentuation of the murmur is absent (even with significant mitral stenosis) in:
  - Rigid or calcified mitral valve
  - Very low cardiac output
  - Atrial fibrillation
- Duration of the murmur is variable. In general, the duration of the murmur correlates with the severity of stenosis (the longer the murmur, the more severe the stenosis).
- The classical diastolic murmur of severe mitral stenosis (mitral valve orifice less than 1 cm^2) starts immediately after the OS, is characteristically long and loud, and present throughout the rest of the diastole with a pre-systolic accentuation, ending in a loud first heart sound.

Murmur of Tricuspid Regurgitation

- This is a loud pansystolic murmur heard at the lower left sternal border. It is accentuated during inspiration (De-Carvallo's sign). This murmur should be differentiated from an organic mitral regurgitation murmur, which could be an associated lesion.

Murmur of Pulmonary Regurgitation (Graham Steell Murmur)

- This is a high-pitched early diastolic decrescendo murmur along the left sternal border. Pulmonary regurgitation results from dilatation of the pulmonary valve ring that occurs with severe pulmonary hypertension. This murmur should be differentiated from the more common mild aortic regurgitation murmur, which could be an associated lesion.

Other Findings

- Tender hepatomegaly, peripheral oedema, ascites and right-sided pleural effusion may occur with severe right ventricular failure.

Signs Indicating Severity of Mitral Stenosis

- Narrow A$_2$–OS interval
- Signs of pulmonary arterial hypertension
- Long diastolic murmur
- Signs of right ventricular overload

Investigations in Mitral Stenosis

- Electrocardiogram can confirm:
  - Left atrial enlargement ("P" mitrale)
  - Right ventricular hypertrophy
  - Atrial fibrillation

Radiological Features of Mitral Stenosis

Due to left atrial enlargement
- Straightening of left heart margin (mitralisation) due to enlargement of left atrial appendage
- Double right heart margin (shadow through shadow or double bubble)
- Widening of carinal angle and elevation of left main bronchus
- Indentation of oesophagus on barium swallow

Due to pulmonary venous hypertension
- Prominence of upper lobe veins (stag's antlers sign or reverse moustache sign)
- Kerley A (straight lines up to 4 cm long, running towards hilum) and Kerley B (short, horizontal lines near costophrenic angles) lines
- Endobronchial cuffing
- Bilateral perihilar opacity dense at the hilum, fading towards periphery (bat's wing sign)

Due to pulmonary arterial hypertension
- Prominent pulmonary conus
- Prominence of pulmonary arteries and their main branches
- Peripheral pruning of the small pulmonary arteries
- Right ventricular enlargement

Due to changes in the mitral valve
- Calcification of the mitral valve, best seen on fluoroscopy

- Echocardiogram can reveal:
  - Mitral stenosis and the valve orifice size
  - Anatomy of the mitral valve apparatus
  - Size of cardiac chambers
  - Pulmonary artery pressure
  - Calcification of mitral valve
  - Other associated valvular lesions
- Transoesophageal echocardiography can reveal:
  - An improved image of mitral valve anatomy including presence of calcification
  - A clot in the left atrium or in the left-atrial appendage
- Cardiac catheterisation:
  - Rarely needed as imaging methods discussed above are accurate.
  - Occasionally used to assess discrepancies between symptoms and echocardiography findings.
  - Occasionally used to image coronary arteries in elderly patients.

Complications of Mitral Stenosis

• Atrial fibrillation	• Winter bronchitis
• Pulmonary hypertension	• Dysphagia due to oesophageal compression by the
• Right ventricular failure	left atrium
• Systemic thromboembolism	• Ortner's syndrome
• Haemoptysis	• Infective endocarditis (very rare)

Atrial Fibrillation in Mitral Stenosis

- Most common complication of mitral stenosis, occurs in up to 40% of patients.
- Atrial fibrillation can occur as a transient episode or a sustained arrhythmia.
- Loss of atrial contraction with the development of atrial fibrillation decreases the cardiac output by 15–20%. Since cardiac output is related to heart rate, atrial fibrillation with a rapid ventricular rate decreases the diastolic filling time and further compromises cardiac output.
- Atrial fibrillation predisposes to systemic embolism.
- The incidence of atrial fibrillation in mitral stenosis is related to:
  - Size of the left atrium (the larger the size, the more frequent)
  - Age of the patient (the older the patient, the more frequent)
  - Residual rheumatic inflammation
  - Left atrial fibrosis

Systemic Embolism in Mitral Stenosis

- Systemic embolism occurs from the clots formed in the left atrium.
- Usually, it is the freshly formed clots that get dislodged, rather than the old ones.
- Embolisation commonly occurs to brain (60–70%), kidneys, spleen and extremities.
- Embolism is more frequent in the following situations:
  - Atrial fibrillation
  - Older patients (above the age of 35 years)
  - Those with reduced cardiac output
  - Those who already had one or more embolic episodes
  - Those having a large left atrial appendage

Infective Endocarditis

- Occurs infrequently in patients with isolated mitral stenosis.
- In patients with mitral stenosis alone, it occurs more frequently in mild mitral stenosis with pliable valves and less frequently in severe stenosis with rigid, calcified valves.

Ortner's Syndrome

- This is a very rare complication of severe pulmonary hypertension secondary to mitral stenosis. There is hoarseness of voice due to paralysis of left recurrent laryngeal nerve. There is compression of the nerve between the enlarged tense pulmonary artery and the aorta, at ligamentum arteriosum.

Management of Mitral Stenosis

Medical Management

- Treatment of atrial fibrillation with anticoagulants, digoxin, verapamil, diltiazem, β-blockers and cardioversion.
- Treatment of right ventricular failure with salt restriction, diuretics, digoxin, etc.
- Infective endocarditis prophylaxis is not recommended in patients with mitral stenosis unless mitral valve replacement or mitral valve repair using prosthetic material has been done or patient had previous endocarditis.
- Rheumatic fever prophylaxis.

Surgical Management

- Indicated in patients with class III or IV symptoms. Other considerations include valve anatomy and onset of complications even in absence of symptoms (e.g. atrial fibrillation, pulmonary arterial hypertension and embolic events).

- Balloon mitral valvotomy (BMV) also known as percutaneous balloon valvuloplasty (PBV) in young patients without extensive valvular calcification or thickening, no atrial thrombus and no or mild mitral regurgitation. Also a procedure of choice in pregnant females.
- Closed surgical mitral commissurotomy (closed mitral valvotomy) is rarely performed as BMV is superior to it.
- Open mitral commissurotomy (open mitral valvotomy).
- Mitral valve replacement is performed if significant mitral regurgitation is present, if leaflets are immobile, heavily calcified or if there is severe subvalvular scarring.
  - Mechanical prosthetic valves: Require lifelong anticoagulation.
    - Types
      - Caged-ball valve (Starr–Edwards prosthesis)
      - Tilting-disc valve (Bjork–Shiley valve)
    - Tilting disc valve preferred as compared to caged-ball valve because:
      - It occupies less space and hence can be used in patients with small left ventricle.
      - Incidence of haemolysis is lower.
      - Incidence of strut fracture is lower.
  - Bioprosthetic valves: Low incidence of thrombosis
    - Types
      - Porcine bioprosthetic valve
      - Pericardial xenograft prosthetic valve
    - Useful in pregnancy when oral anticoagulants are contraindicated
    - Because of rapid deterioration of valve it is not used in young patients <35 years of age.

Q. How will you clinically differentiate between mitral opening snap (OS) and split second heart sound (split S_2)?

- Particularly when the OS is heard at the pulmonary area, it has to be differentiated from a split second sound. The question is whether the second component is P_2 or OS. The differentiation is based on the character and behaviour of the second component as well as the split.

Mitral opening snap (OS)	Split second sound (split S_2)
• OS is high pitched and loud	• P_2 is soft, unless accentuated
• OS best-heard medial to apex	• P_2 best heard at pulmonary area
• Split widens on standing (A_2–OS interval increases)	• Split narrows on standing (A_2–P_2 interval decreases)
• Split narrows on inspiration	• Split widens on inspiration
• OS is louder during expiration	• P_2 is louder during inspiration
• Intensity of OS is unchanged on leg raising	• Intensity of P_2 is louder on leg raising
• Loud S_1 and other evidences of MS	• S_1 may or may not be loud

Q. How will you differentiate between the mitral opening snap (OS) and left ventricular third heart sound (S_3)?

- The mitral opening snap (OS) and third heart sound (S_3) occur in early diastole. At times, it becomes difficult to differentiate between the two.

Mitral opening snap (OS)	Left-sided third heart sound (S_3)
• High-pitched, sharp, snappy sound	• Low-pitched thud or boom
• Best heard medial to the apex	• Best heard at the apex
• May be heard extensively along the left sternal edge or at the base of the heart	• Well localised to the apex
• Best heard with the diaphragm of the stethoscope left	• Best heard with the bell piece of the stethoscope, with the patient in the left lateral position
• Less widely separated from S_2 (A_2–OS interval is 0.04–0.12 s)	• More widely separated from S_2 (A_2–S_3 interval is 0.14–0.16 s)

• Separates further from A_2 on standing (A_2–OS interval increases)	• Does not move on standing (A_2–S_3 interval is unchanged)
• Louder during expiration	• Decreases during inspiration
• Intensity unchanged with leg raising and sustained hand grip	• Intensity increases with leg raising and sustained hand grip
• Usually associated with a loud S_1 and other evidence of MS	• May or may not be associated with a loud S_1

Q. Discuss the aetiology, pathophysiology, clinical features, investigations, complications and management of chronic mitral regurgitation. How do you clinically assess the severity of mitral regurgitation?

Q. What are the causes of acute mitral regurgitation?

Aetiology

Chronic Mitral Regurgitation

Common causes	Less common causes
• Rheumatic heart disease (40%)	• Congenital mitral regurgitation
• Rupture of chordae tendineae (20%)	• Ischaemia or infarction of myocardium
• Degenerative mitral valve disease, e.g. mitral valve prolapse (15%)	• Marked LV enlargement of any cause
• Ischaemic papillary muscle dysfunction (10%)	• Cardiomyopathies (dilated and hypertrophic)
• Infective endocarditis (5%)	• Mitral annulus calcification
	• Systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis
	• Marfan's syndrome

Acute Mitral Regurgitation

• Infective endocarditis
• Acute myocardial infarction with rupture of a papillary muscle or one of its heads
• Chest trauma
• Cardiac surgery
• Acute rheumatic fever with carditis
• Prosthetic valve dysfunction

Rheumatic Mitral Regurgitation

• Commonest cause of chronic mitral regurgitation in India.
• Pure or predominant mitral regurgitation is more common in males.
• Rheumatic involvement of mitral valve causes marked fibrosis, thickening, calcification and shortening of both mitral leaflets and chordae tendineae. These result in improper closure of valve cusps during systole resulting in mitral regurgitation.

Organic Versus Functional Mitral Regurgitation

• Functional mitral regurgitation (MR) is caused by both ischaemic (coronary artery disease) and non-ischaemic heart diseases (e.g. dilated cardiomyopathy) via multiple mechanisms including impaired left ventricular wall motion, left ventricular dilatation, and papillary muscle displacement and dysfunction. Here the valve is normal.
• Organic MR is caused by structural abnormalities of valve leaflets and sub valvular apparatus, including stretching or rupture of chordae tendineae.

Pathophysiology of Acute Mitral Regurgitation

• With sudden onset of mitral regurgitation, the regurgitant blood flows into small, non-compliant left atrium causing acute elevation of left atrial pressure and pulmonary arterial pressure.
• Left ventricle is unable to effectively increase cardiac output.
• Both these factors lead to acute pulmonary oedema and cardiogenic shock.

Pathophysiology of Severe Chronic Mitral Regurgitation

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┌─────────────────────────┐
│   Mitral regurgitation  │
└─────────────────────────┘
              │
              ▼
┌───────────────────────────────────┐      ┌───────────────────────────────────┐
│ Part of left ventricular blood    │─────▶│ Corresponding reduction of volume │
│ regurgitates into left atrium     │      │ of blood ejected into aorta       │
│ during systole                    │      │                                   │
└───────────────────────────────────┘      └───────────────────────────────────┘
              │                                           │
              ▼                                           │
┌───────────────────────────────────┐                    │
│ Left atrial blood volume increases│                    │
│ Left atrial size increases        │                    │
│ ("giant" left atrium)             │                    │
└───────────────────────────────────┘                    │
              │                                           │
              ▼                                           │
┌───────────────────────────────────┐                    │
│ Volume of blood returning         │                    │
│ from left atrium to left          │                    │
│ ventricle is increased            │                    │
└───────────────────────────────────┘                    │
              │                                           │
              ▼                                           │
┌───────────────────────────────────┐                    │
│ Diastolic overfilling of left     │                    │
│ ventricle                         │                    │
└───────────────────────────────────┘                    │
              │                                           │
              ▼                                           │
┌───────────────────────────────────┐                    │
│ Left ventricular hypertrophy and  │                    │
│ dilatation                        │                    │
└───────────────────────────────────┘                    │
              │                                           ▼
              ▼                              ┌───────────────────────────────┐
┌───────────────────────────┐               │ Reduction in cardiac output   │
│ Left ventricular failure  │               └───────────────────────────────┘
└───────────────────────────┘
              │
              ▼
┌───────────────────────────┐
│ Pulmonary hypertension    │
└───────────────────────────┘
              │
              ▼
┌───────────────────────────┐
│ Right ventricular failure │
└───────────────────────────┘
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- In chronic mitral regurgitation, atrium is more compliant, and therefore mechanical energy generated by left ventricle causes volume overload and atrial enlargement rather than an increase in intra-atrial pressure.
- Patients with chronic mitral regurgitation often remain asymptomatic for many years. Over time, however, the left ventricle dilates to accommodate increased volume load and maintains cardiac output. Chronic left ventricular volume overload leads to contractile dysfunction, heart failure and increased risk of sudden death.

Clinical Features

Symptoms

- Patients with chronic mitral regurgitation may remain asymptomatic for several years.
- Palpitation is the most common symptom.
- Symptoms of reduced cardiac output like fatigability, weakness, exhaustion, weight loss and cachexia are common.
- Symptoms of left ventricular failure like exertional breathlessness, orthopnoea and paroxysmal nocturnal dyspnoea occur late in the course of mitral regurgitation.
- Features of right-sided heart failure like tender hepatomegaly, peripheral oedema, raised jugular venous pressure, ascites and functional tricuspid regurgitation are uncommon, and occur very late in the course of mitral regurgitation. They are seen in patients with pulmonary hypertension.
- In acute mitral regurgitation the symptoms are due to acute pulmonary oedema.
- In severe mitral regurgitation sudden death may occur with rupture of chordae tendineae which causes about 25% of deaths of patients on medical treatment.

Signs

- Pulse
  - High volume that in severe mitral regurgitation may become collapsing.
  - Irregular rhythm and varying volume in atrial fibrillation associated with long-standing mitral regurgitation.
- Jugular veins
  - JVP is normal in uncomplicated mitral regurgitation.
  - With atrial fibrillation, *a* waves disappear. With pulmonary hypertension, *a* waves are more prominent.
  - With right ventricular failure and functional tricuspid regurgitation, jugular venous pressure is raised and *v* waves become very prominent.

- Blood pressure
  - Wide pulse pressure in severe mitral regurgitation.

Inspection and Palpation

- "Rocking motion of the precordium" with each cardiac cycle due to a combination of retraction of the left ventricle and expansion of the left atrium during systole.
- Apex beat is shifted downwards and laterally, and is hyperdynamic (forceful but ill-sustained) in character.
- Systolic thrill at the apex.
- Sustained left parasternal heave and palpable pulmonary component of second heart sound (P_2) in pulmonary hypertension.

Auscultation

- First heart sound (S_1) is usually soft.
- In severe mitral regurgitation the second heart sound (S_2) is widely split due to aortic valve closure (A_1) occurring early.
- Pulmonary component (P_2) of S_2 is loud in pulmonary hypertension.
- Left ventricular third heart sound (S_3) may be present in severe mitral regurgitation.
- Pulmonary ejection sound in pulmonary hypertension.

Murmur of Mitral Regurgitation

- The typical murmur of chronic mitral regurgitation is high pitched, blowing and usually pansystolic best heard at the apex, commonly radiating to the axilla and left interscapular area.
- In those patients with mitral regurgitation secondary to anterior mitral leaflet involvement the murmur radiates to axilla and back. In those with posterior mitral leaflet involvement it radiates to the left sternal border and base of heart.
- Since the rheumatic mitral valve damage predominantly affects the anterior mitral leaflet, most of the rheumatic mitral regurgitation murmurs radiate to the axilla and back (interscapular area).
- In patients with ruptured chordae tendineae, the murmur has a "cooing" or "sea gull" quality.
- In patients with flail mitral leaflet, the murmur has a "musical" quality and is late systolic.

Mitral Flow Murmur

- A short, rumbling mid-diastolic murmur may be audible at the apex in severe cases due to an increased flow across the mitral valve.

Other Murmurs

- Ejection systolic murmur at pulmonary area due to pulmonary hypertension.
- Pansystolic murmur at lower-left sternal border due to functional tricuspid regurgitation.

Signs Indicating Severity of Mitral Regurgitation

- High volume pulse - Cardiomegaly with hyperdynamic apex - Left ventricular third heart sound (S_3)	- Wide mobile split of second heart sound (S_2) - Loud pansystolic murmur - Mid-diastolic flow murmur at apex

Signs in Acute Mitral Regurgitation

- Normal apical impulse as ventricle is not yet dilated
- Third heart sound and/or fourth heart sound
- An early systolic or pansystolic murmur

Investigations

- Electrocardiogram can detect the following abnormalities:
  - Left atrial enlargement
  - Left ventricular dilatation and hypertrophy
  - Biventricular hypertrophy in pulmonary hypertension
  - Atrial fibrillation
- Chest radiography might show the following abnormalities:
  - Cardiomegaly with left atrial and left ventricular enlargement
  - "Giant left atrium"
  - Calcification of mitral valve
- Doppler echocardiogram can detect the following abnormalities:

- Enlarged left atrium
- Hyperdynamic left ventricle
- Degree of mitral regurgitation
- Clues regarding the aetiology of mitral regurgitation
- Barium swallow might show left atrial enlargement as a posterior displacement of oesophagus in the right anterior oblique view.

Complications

- Progressive heart failure is the most common cause of death in these patients.
- Sudden death, stroke and fatal endocarditis are less frequent.

• Atrial fibrillation	• Pulmonary hypertension (late)
• Infective endocarditis	• Right ventricular failure (very late)
• Left ventricular failure	• Systemic embolism (rare)

Management

- Medical management
  - Infective endocarditis prophylaxis is not indicated in patients with mitral regurgitation. However, it is mandatory for patients after mitral valve repair or after mitral valve replacement (MVR).
  - Rheumatic fever prophylaxis.
  - Restriction of physical activity.
  - Evaluation and modification of coronary artery disease risk factors to prevent its development.
  - Follow-up asymptomatic patients with echocardiography in order to assess left ventricular dilatation and systolic dysfunction.
  - Treatment of heart failure with salt restriction, digoxin, diuretics, ACE inhibitors, β-blockers, aldosterone antagonists and vasodilators.
  - Treatment of atrial fibrillation with digoxin, verapamil, anticoagulation and cardioversion.
  - In acute mitral regurgitation, nitrates and diuretics to reduce filling pressures.
- Surgical management
  - Re-construction of mitral valve apparatus by mitral valvuloplasty or mitral annuloplasty. Preferred to MVR whenever feasible.
  - MVR with a prosthesis.
- Indications for surgery
  - Acute mitral regurgitation
  - Chronic severe mitral regurgitation and NYHA functional class II, III or IV symptoms in the absence of severe left ventricular dysfunction (defined as ejection fraction <30% and/or left ventricular end-systolic dimension >55 mm).
  - Asymptomatic or symptomatic patients with mild (EF ≤60% and left ventricular end systolic diameter 45–50 mm) or moderate (EF 30–50% and left ventricular end systolic diameter 50–55 mm) left ventricular dysfunction.
  - Asymptomatic severe mitral regurgitation with normal left ventricular size and function (ejection fraction >60% and left ventricular end-systolic dimension <45 mm), only if likelihood of successful mitral valve repair is high.

Q. In the presence of combined mitral stenosis and mitral regurgitation, how will you clinically assess the dominance of lesions?

Signs of predominant mitral regurgitation	Signs of predominant mitral stenosis
• High volume pulse	• Low volume pulse
• Left ventricular enlargement	• Evidence of right ventricular hypertrophy
• Hyperdynamic apex	• Evidence of pulmonary hypertension
• Soft first heart sound	• Loud first heart sound
• Wide splitting of second heart sound	• Narrow splitting of second heart sound
• Left ventricular third heart sound	• Distinct OS with a narrow A_2–OS interval
• Short mid-diastolic flow murmur	• Long mid-diastolic murmur with presystolic accentuation

Q. Discuss the aetiology, clinical features, complications and management of mitral valve prolapse (MVP) or Barlow's syndrome.

- Mitral valve prolapse (MVP) is an abnormal systolic valve movement of one or both of the mitral leaflets towards the left atrium ($\geq$2 mm beyond annular plane). Thus in MVP mitral leaflets bulge into the left atrium during ventricular systole, with or without mitral regurgitation.

Aetiologic Considerations

- More common in females between 15 and 30 years; however, severe mitral regurgitation caused by prolapse is more frequent in older males than young females.
- Redundant mitral leaflet tissue and chordae tendineae.
- Structural abnormalities causing mitral prolapse include diffuse myxomatous degeneration of mitral valve and primary flail leaflet with ruptured chords. These conditions predominantly affect the posterior mitral leaflet.
- Familial incidence with an autosomal dominant mode of inheritance.
- Commonly associated with Marfan's syndrome and cystic medial necrosis.
- MVP may be associated with the following conditions:
  - Congenital heart diseases, especially atrial septal defect
  - Acute rheumatic fever, chronic rheumatic heart disease
  - Ischaemic heart disease, cardiomyopathies

Clinical Features

Symptoms

- Asymptomatic
- Atypical chest pain (precordial, stabbing)
- Palpitation (due to ventricular ectopics, supraventricular tachycardia, ventricular tachycardia)
- Syncope or presyncope (light headedness, dizziness)
- Orthostatic phenomena (orthostatic tachycardia, hypotension and arrhythmias)
- Fatigue
- Rarely, symptoms of left ventricular failure like exertional dyspnoea, orthopnoea and paroxysmal nocturnal dyspnoea in patients with severe mitral regurgitation
- Rarely, sudden death
- Rarely, transient ischaemic attacks

Signs

- Abnormalities of chest wall and thoracic spine (scoliosis, narrow anteroposterior chest diameter, straight back or pectus excavatum)
- Bifid apical impulse
- Mid or late systolic click(s)—occur $\geq$0.14 seconds after S_1 (non-ejection click)
- Mid-systolic or late systolic apical murmur (rarely "whooping" or "honking") may or may not be present
- The systolic murmur of mitral valve prolapse increases during standing and Valsalva manoeuvre, but decreases during squatting and isometric exercise

- Click results from a sudden tensing of mitral valve apparatus as the leaflets prolapse into left atrium.
- When end-diastolic volume is decreased (as with standing), click–murmur complex occurs shortly after S_1. Manoeuvres that increase end-diastolic volume (such as squatting) cause click–murmur complex to move toward S_2.

Investigations

- Electrocardiogram usually shows non-specific ST–T changes in leads II, III and aVF.
- Echocardiography can confirm the diagnosis. Serial echocardiography is usually not necessary unless mitral regurgitation is present.
- Colour Doppler to assess mitral regurgitation.

Complications

- Arrhythmias
- Infective endocarditis
- Progressive mitral regurgitation
- Transient cerebral ischaemic attacks and embolic episodes (rare)
- Acute severe mitral regurgitation (rare)
- Sudden death (rare)

Management

- Reassurance of asymptomatic patients
- Infective endocarditis prophylaxis is not recommended
- β-blockers in atypical chest pain
- Antiarrhythmic drugs in arrhythmias
- Aspirin, dipyridamole or anticoagulants in transient ischaemic attacks
- Mitral valve repair or replacement in severe mitral regurgitation (defined as symptomatic patient or EF <60% with left ventricular end systolic diameter >45 mm)

Q. Classify aortic stenosis. Discuss the aetiology, clinical features, investigations and management of valvular aortic stenosis.

Classification

- Valvular aortic stenosis
- Subvalvular aortic stenosis
- Supravalvular aortic stenosis

Aortic Valve

- The normal aortic valve area averages 3–4 cm^2, and there should normally be minimal gradient across it (<10 mmHg).
- A valve area of less than 0.8 cm^2 or a gradient of more than 50 mmHg represents critical stenosis.

Aetiology of Aortic Stenosis

Valvular aortic stenosis	Subvalvular aortic stenosis
- Acquired	- Membranous diaphragm
- Rheumatic heart disease	- Tunnel deformity
- Fibrocalcific deformity of a bicuspid valve	- Hypertrophic cardiomyopathy
- Fibrocalcific deformity of three cusped valve or calcific stenosis of a trileaflet aortic valve (aortic sclerosis)	**Supravalvular aortic stenosis**
- Systemic lupus erythematosus (SLE)	- Hourglass constriction of aorta
- Fabry's disease	- Hypoplasia of aorta
- Type II hyperlipoproteinaemia	- Fibromembranous lesion of aorta
- Infective endocarditis	
- Radiation exposure	
- Congenital	
- Unicuspid unicommissural valve	
- Three cusped valve with fusion of commissures	
- Hypoplastic annulus	

Clinical Features

Symptoms

- Natural history characterised by years of asymptomatic progression.
- Decreased exercise tolerance is usually the first symptom and occurs due to angina in the compensated phase (average survival 4 years).
- Exertional dizziness and syncope (average survival 3 years).

- Exertional breathlessness, orthopnoea and paroxysmal nocturnal dyspnoea due to heart failure which occurs in the decompensated phase (average survival 2 years).
- Haematemesis and melaena from AV malformations of right colon, small intestine and stomach (Heyde's syndrome).

Signs

- Pulsus tardus is a slow rising arterial pulse best felt in carotids (delayed carotid upstroke) due to prolongation of ejection phase. The classic anacrotic pulse is seen in severe aortic stenosis.
- Low systolic blood pressure (<100 mmHg).
- In congenital supravalvular aortic stenosis, systolic blood pressure is usually higher by approximately 30 mmHg in right arm than in left arm.
- Normal jugular venous pulse; however prominent *a* waves may be present due to reduced right ventricular compliance produced by hypertrophy of interventricular septum.
- Systolic thrill in carotids.
- Systolic thrill at aortic area radiating to carotids, lower-left sternal border and even mitral area (cross-belt area).
- Heaving apical impulse.
- No cardiomegaly in the initial stages of concentric hypertrophy. Cardiomegaly develops later, with left ventricular dilatation and failure.

Auscultation

- The aortic component of second heart sound (A_2) is delayed, resulting in a narrow splitting of second heart sound in mild to moderate aortic stenosis, and a paradoxical splitting of second heart sound in severe aortic stenosis.
- Intensity of A_2 component is decreased and may even be inaudible, when the second heart sound appears single (single S_2). In congenital valvular aortic stenosis, A_2 is usually heard as the valve remains flexible.
- Ejection click is of valvular origin in young patients where the valve is not immobilised by calcification. It does not vary with respiration.
- Left ventricular third heart sound (LVS_3) in left ventricular failure.
- Fourth heart sound due to vigorous atrial contraction.
- The murmur of aortic stenosis is an ejection systolic murmur (ESM) best heard at aortic area, conducted to carotids. It is best heard with the patient sitting up, leaning forwards and breath held in expiration.
  - Soft, short ESM with early peaking suggests mild stenosis.
  - Harsh, loud, long ESM with late peaking suggests severe stenosis.
  - At times, as one moves downwards from aortic area to mitral area, the murmur initially becomes softer and then again increases in intensity. This phenomenon is known as "hourglass conduction".
  - In calcific aortic stenosis, the murmur is loud and harsh in the aortic area, but it has a musical quality along the left sternal border and at apex. This difference in quality of the same murmur at two different sites is referred to as "Gallavardin phenomenon". It may be confused with murmur of mitral regurgitation. However, the murmur of aortic stenosis at apex is musical and high pitched while that of mitral regurgitation is harsh holosystolic murmur.
- In congenital subvalvular stenosis, aortic regurgitation may develop producing a diastolic murmur.

Supravalvular Aortic Stenosis

- Narrowing of ascending aorta that can occur as a discreet hourglass deformity or as a diffuse hypoplasia originating at the superior margin of the sinuses of Valsalva just above the level of the coronary arteries.
- Narrowing of several other arteries often present. This includes narrowing of peripheral pulmonary arteries (peripheral pulmonary artery stenosis), and narrowing of other arteries like coronary, renal, carotid, innominate and mesenteric arteries. Coarctation of aorta may also be present.
- Sporadic or familial; in later form, it is transmitted as an autosomal dominant trait with incomplete penetrance and variable expressivity.
- Asymptomatic or presentation with dyspnoea, chest pain due to aortic stenosis with coronary abnormalities, myocardial infarction, stroke or even sudden death occurring during exercise. Infants may present with features of heart failure.

Examination

- Systolic murmur and thrill, best at the first right intercostal space.
- No ejection sound (in contrast to aortic valve stenosis).

- Continuous murmur if peripheral pulmonary artery stenosis is present.
- Disparity of pulse and blood pressure between the arms due to selective streaming of blood into innominate artery (blood pressure in right arm may exceed the pressure in the left one by 20 mmHg or more).
- Femoral pulse reduced if coarctation of aorta also present.
- Hoarse voice, hernias, lax skin, stiffness of joints due to deficient elastin.

Williams Syndrome

- Comprises of several features.
  - Supravalvular aortic stenosis.
  - Elfin facies (prominent forehead, widely spaced eyes, upturned nose, underdeveloped mandible, dental hypoplasia, patulous lips).
  - Mental retardation.
  - Hypercalcaemia.

Investigations

- Chest radiography
  - Normal heart size (due to concentric hypertrophy of left ventricle in initial stages)
  - Post-stenotic dilatation of aorta
  - Calcification of aortic valve (best appreciated in lateral X-ray)
- ECG shows left ventricular hypertrophy with or without strain, first-degree AV block or bundle branch block
- Echocardiography
  - Accurate assessment of aortic valve area
  - Number of aortic valve cusps
  - Pattern of thickening of aortic cusps
  - Transvalvular gradient
  - Left ventricular hypertrophy and ejection fraction
- Exercise stress testing and serum brain natriuretic peptide (BNP) level may help determine the appropriateness of valve replacement in asymptomatic patients with severe aortic stenosis.
- Cardiac catheterisation with coronary angiography before aortic valve surgery

Treatment

- No strenuous physical work
- Avoid hot baths, steam rooms and saunas so as to avoid hypotension that may result from peripheral vasodilation.
- Infective endocarditis prophylaxis in patients who have undergone aortic valve replacement. It is not recommended for patients with aortic stenosis or other acquired valve diseases. Absolute risk of endocarditis is sufficiently low (well under 1% per year) and therefore, the benefit of antibiotic prophylaxis before any invasive procedure does not outweigh the risk.
- Rheumatic fever prophylaxis in aortic stenosis of rheumatic aetiology.
- Treatment of angina, atrial fibrillation and left ventricular failure.
- Treatment of systemic hypertension with ACE inhibitors. Nitrates should be used with caution in patients with angina as this may lead to orthostatic hypotension and syncope. β-blockers are avoided because the patient may be critically sensitive to a small fall in contractility in the presence of tight aortic stenosis.
- For asymptomatic patients with preserved LV ejection fraction, follow-up echocardiographs to monitor the gradient and LV systolic function every 3 to 5 years for mild aortic stenosis and every 6 to 12 months for severe aortic stenosis.
- Surgery
  - Surgery is advised when the patient has moderately severe aortic stenosis with symptoms or signs of left ventricular failure. It is also recommended in severe aortic stenosis with ejection fraction <50%, patients with moderate or severe aortic stenosis undergoing other cardiac surgery, and presence of dilated aortic root.
  - Open commissurotomy or valvuloplasty for non-calcific stenosis.
  - Aortic valve replacement (open or transcutaneous aortic implantation—TAVI) for calcific aortic stenosis.
- Percutaneous balloon valvotomy generally not useful:
  - High risk for stroke, aortic regurgitation, and other complications
  - High risk for re-stenosis

Q. What is the mechanism of angina in aortic stenosis?

- Increase in left ventricular muscle mass leads to increased oxygen demand.
- Left ventricular systolic hypertension leads to increase in myocardial oxygen need and impedance in systolic coronary flow.
- Prolongation of systole leads to increased myocardial oxygen consumption.
- Limiting the duration of diastole leads to reduced coronary filling.
- Coronary atherosclerosis.

Q. How will you clinically assess the severity of aortic stenosis?

- Severe aortic stenosis is characterised by one or more of the following:

• Low systolic blood pressure	• Paradoxical splitting of S_2
• Heaving apical impulse	• Harsh, loud, long ejection systolic murmur with late peaking
• Soft A_2 or single S_2	• Orthopnoea, paroxysmal nocturnal dyspnoea, cardiomegaly and S_3

Q. Discuss briefly about aortic sclerosis.

- Defined as thickening and calcification of a tricuspid (three cusps) aortic valve without any obstruction to left ventricular outflow.
- Fairly common in elderly people, affecting 21–26% of adults aged >65 years.
- Patients asymptomatic.
- Examination may show a soft systolic murmur at the aortic area, a normal split of second heart sound, and a normal volume carotid pulse.
- Risks
  - Progression to aortic stenosis (calcific aortic valve disease): Risk factors like hypercholesterolaemia, raised lipoprotein Lp(a), smoking, hypertension and diabetes increase the rate of progression to calcific aortic stenosis. These factors are also associated with higher frequency of aortic sclerosis without aortic stenosis in a given population.
    - Aortic sclerosis may be accompanied by mitral annulus calcification (up to 50%).
    - Increased cardiovascular morbidity and mortality possibly due to increased rate of atherosclerosis.
    - Development of aortic regurgitation is rare.
- Diagnosed by echocardiography that shows leaflet thickening, stiffness and increased echogenicity with normal excursion of leaflets. The commissures are not fused.
- Quantification of aortic valve calcification by electron-beam tomography; using this technique, valve calcification can be sequentially monitored.
- Treatment
  - No medical treatment of proven efficacy.
  - Experimental therapies include use of HMG Co-A inhibitors (statins) to slow the progress of calcification and ACE inhibitors.

Q. Write a short note on bicuspid aortic valve disease.

- Most common congenital cardiac defect
- Male to female ratio of 3:1
- Often associated with other congenital cardiac lesions, most frequent being dilatation of proximal ascending aorta secondary to abnormalities of the aortic media. Others include coarctation of aorta, hypoplastic left heart syndrome, ventricular septal defect (VSD), atrial septal defect.
- Symptoms often develop in adulthood, although the patient may remain asymptomatic throughout his life.
- Complications include aortic valve stenosis, aortic regurgitation, endocarditis, aortic aneurysm formation and aortic dissection.
- Auscultatory findings include an ejection sound best heard at the apex. There may be associated murmurs of aortic stenosis or aortic regurgitation.
- Despite potential complications, life-expectancy is usually not shortened.
- Diagnosis by echocardiography. Calcification is common in adults with bicuspid aortic valve. Cardiac MRI augments the diagnostic process as it enables views of the valve without interference from calcification. It also allows for excellent assessment of the aorta.
- Medical management includes control of hypertension and use of β-blockers. Surgical treatment includes aortic valve replacement. Many will also need aortic root surgery.

Q. Discuss the aetiology, clinical features, complications, investigations and treatment of aortic regurgitation.

Q. What are the peripheral signs of aortic regurgitation?

- Aortic regurgitation can be acute or chronic.

Aetiology

Acute aortic regurgitation	Chronic aortic regurgitation	
	Common causes	**Uncommon causes**
• Trauma	• Rheumatic (two-third of cases)	• Infective endocarditis
• Rheumatic fever	• Syphilis	• Ventricular septal defect (VSD)
• Infective endocarditis	• Bicuspid aortic valve	• Marfan's syndrome
• Dissecting aneurysm	• Atherosclerotic aortic valve	• Rheumatoid arthritis
		• Ehlers–Danlos syndrome
		• Systemic lupus erythematosus
		• Ankylosing spondylitis
		• Reiter's syndrome
		• Takayasu's disease
		• Aneurysm of aorta
		• Severe hypertension

Pathophysiology

- In chronic aortic regurgitation left ventricle enlarges producing a greater total stroke volume, which is ejected into aorta. With progression there is decline in left ventricular function that causes left ventricle to dilate, leading to increase in left ventricular end-diastolic volume without further elevation of the regurgitant volume. Ultimately, ejection fraction and forward stroke volume decline during rest and ventricular emptying is impaired. In advanced stages left atrium pressure, pulmonary artery wedge pressure, pulmonary artery pressure, and right atrium pressure rise and cardiac output falls.
- In cases of acute aortic regurgitation left ventricle does not have time to adapt to increased diastolic volume. Thus, the patient develops acute left ventricular failure without typical high cardiac output state.

Clinical Features

Symptoms

- Remain asymptomatic for years or decades, but once decompensated, they deteriorate rapidly
- Palpitations, forceful pulsations in the neck
- Angina
- Exertional breathlessness, orthopnoea and paroxysmal nocturnal dyspnoea
- Syncope
- Symptoms of right ventricular failure (late)

Signs

Peripheral Signs of Aortic Regurgitation

Sign	Feature
• Collapsing pulse (water–hammer pulse)	Best appreciated on the radial artery when the arm is elevated. This is characterised by a rapid upstroke, rapid down stroke and a high volume
• Corrigan's pulse	A jerky carotid pulse characterised by full expansion followed by quick collapse
• Pulsus bisferiens	Best felt in the carotids. This is a pulse with double peak (two peaks), both being felt in systole. It is seen in severe aortic regurgitation

Sign	Feature
• Wide pulse pressure	Results from a low diastolic pressure from aortic run-off and high systolic pressure from increased stroke volume (on auscultation, Korotkoff sounds may disappear at a low point, may be even 0 mmHg; phase IV may be taken as indicative of diastolic pressure)
• Hill's sign	Popliteal cuff systolic pressure exceeding brachial cuff systolic pressure by more than 20 mmHg (measured manually) • A difference of 20–39 mmHg indicates mild aortic regurgitation (AR) • A difference of 40–59 mmHg indicates moderate AR • A difference of 60 mmHg or more indicates severe AR
• Corrigan's neck sign	Prominent carotid pulsations visible in the neck
• De-Musset's sign	Anteroposterior motion of the head (head nodding) synchronous with cardiac cycle
• Landolfi's sign	Alternating dilatation and constriction of pupil synchronous with cardiac cycle
• Muller's sign	Pulsations of the uvula
• Lighthouse sign	Capillary pulsations on the forehead and face resulting in alternate blanching and flushing
• Quincke's sign	Alternate paling and flushing of lightly compressed nail bed or mucous membrane of mouth
• Rosenbach's sign	Pulsations of the liver
• Gerhardt's sign	Pulsations of an enlarged spleen
• Pistol-shot femorals	Booming sound synchronous with systole heard over the femoral arteries
• Traube's sign	Booming systolic and diastolic sounds heard over the femoral artery
• Duroziez sign	A systolic murmur heard over the femoral artery when it is compressed proximally and a diastolic murmur when it is compressed distally
• Mayne sign	More than a 15-mmHg decrease in diastolic blood pressure with arm elevation from the value obtained with the arm in the standard position
• Rosenbach sign	Pulsatile liver
• Becker sign	Accentuated retinal artery pulsations
• Gerhard sign	Pulsatile spleen

Inspection and Palpation

- Prominent neck pulsations
- Thrill in the carotids
- Hyperdynamic precordium
- Hyperdynamic apex that is shifted down and out
- Suprasternal pulsations

Auscultation

- First heart sound (S_1) may be soft.
- A_2 component of second heart sound (S_2) is soft in rheumatic aortic regurgitation (AR), but loud and "tambour" like in syphilitic AR.
- Narrowly split, single or paradoxically split second heart sound
- Third heart sound (S_3) in patients with left ventricular failure
- Fourth heart sound (S_4) in prominent left ventricular hypertrophy
- Early diastolic murmur (EDM) of aortic regurgitation—A high pitched, early diastolic, decrescendo murmur best heard at Erb's area or neo-aortic area (left third intercostal space near sternum) in rheumatic AR and at aortic area in syphilitic AR. The

murmur is best heard with the diaphragm of the stethoscope, with the patient sitting up and leaning forwards, breath held in deep expiration and hands clenched. Rheumatic AR murmur is soft blowing in character. The character of syphilitic AR murmur is described as "cooing dove" or "seagull". A similar character is seen also in AR of infective endocarditis and trauma.

- Ejection systolic murmur—An ejection systolic murmur is heard at aortic area or Erb's area, which might even be conducted to carotids. This is a flow murmur due to increased flow across the aortic valve, and not due to organic aortic stenosis. This murmur may be quite loud. It is often higher-pitched, shorter and less taping in quality than the ejection systolic murmur of aortic stenosis.
- Mid-diastolic murmur (Austin Flint murmur)—A mid-diastolic rumbling murmur is heard at the apex in severe AR. It is a functional murmur and does not represent mitral stenosis.
- A blowing, pansystolic murmur, often radiating to the axilla may be heard at the apex. It is due to marked dilatation of left ventricle and functional mitral regurgitation.

Duroziez Sign

- Elicited by compression of femoral artery with cephalad and caudad tilting of the stethoscope
- Produces systolic and diastolic murmurs
- Systolic portion of the murmur caused by increased forward flow into the lower extremity
- Diastolic murmur caused by aortic regurgitation (backward flow)

Acute Aortic Regurgitation

- Onset is sudden with patient presenting with acute left ventricular failure.
- Pulse pressure is normal with near normal systolic and diastolic pressures.
- Apical impulse is usually not hyperdynamic.
- S_1 is soft or absent.
- P_2 is normal or increased.
- S_3 is commonly heard.
- Early diastolic murmur is short, while functional systolic murmur across aortic valve is less loud.
- Austin Flint murmur is usually absent.
- ECG and chest radiograph generally do not show evidence of left ventricular enlargement.
- Pulmonary venous hypertension in the form of redistribution of upper lobe vessels seen on chest radiograph.

Acute vs. Chronic Aortic Regurgitation

Feature	Acute AR	Chronic AR
Pulse pressure	• Normal or reduced	• Increased
Blood pressure	• Normal or near-normal	• Elevated systolic and diminished diastolic
Apex	• Normal in position and character	• Shifted down and out, hyperdynamic
S_1	• Soft	• Normal or diminished
S_2	• Normal or loud P2	• Narrow split
S_3	• Present	• Absent
Murmurs	• Soft, early diastolic	• Decrescendo or holo diastolic
	• Functional systolic murmur soft	• Functional systolic murmur loud
ECG	• No left ventricular hypertrophy	• Left ventricular hypertrophy
Chest x-ray	• Normal cardiac shadow	• Enlarged cardiac shadow due to left ventricular dilatation
	• Pulmonary venous hypertension	• Pulmonary venous hypertension uncommon

Investigations

- VDRL and TPHA to rule out syphilitic aetiology.
- RA factor, ANA, ESR and CRP to exclude connective tissue disorders.
- ECG shows diastolic overload pattern of left ventricle (LV hypertrophy with ST depression and T inversion in I, aVL, V_5, and V_6).

- Chest radiograph shows gross cardiomegaly of left ventricular type (cor bovinum) and evidence of pulmonary oedema. In bicuspid aortic valve or rheumatic cause of aortic stenosis, calcification of aortic valve may be seen. In syphilitic AR, calcification of ascending aorta may occur.
- Echocardiography—For diagnosis, severity, possible cause, and left ventricular function.
- Doppler echocardiography to assess the severity.
- Cardiac catheterisation.
- Coronary angiography.

Treatment

- Treatment of the underlying cause
- Infective endocarditis prophylaxis is not indicated
- Rheumatic fever prophylaxis
- Medical treatment of cardiac failure with digoxin, diuretics, salt restriction and fluid restriction
- Afterload reduction therapy
  - Isosorbide dinitrate 20–40 mg 6 hourly
  - Hydralazine 50 mg 6 hourly
  - Captopril 25–50 mg 8 hourly or enalapril 5–10 mg twice daily
- Asymptomatic patients with normal left ventricular (LV) size and systolic function do not require surgery but should be monitored carefully for development of symptoms, LV dysfunction or progressive LV dilatation.
- Surgical therapy is required in symptomatic patients or those with LV ejection fraction <50% or end-systolic LV diameter >55 mm (even if asymptomatic). It involves aortic valve replacement (open or TAVI).

Q. Explain the clinical assessment of severity of aortic regurgitation.

- The presence of one or more of the following suggests that AR is severe:

- Presence of peripheral signs	- Hyperdynamic apex, shifted down and out
- Pulsus bisferiens	- Early diastolic murmur (EDM) lasting more than two-third of diastole
- Hill's sign more than 60 mmHg	- Presence of Austin Flint murmur

Q. Describe angina in aortic regurgitation.

Q. What is nocturnal angina?

- Angina is a common symptom in AR, particularly of syphilitic aetiology.
- "Nocturnal angina" is an unusual form of angina occurring in aortic regurgitation. It is characterised by paroxysmal, nocturnal anginal pains associated with nightmares, dyspnoea, palpitations, skin flushing, profuse sweating and wide pulse pressure. It does not respond to sublingual nitroglycerine.

Mechanisms of Angina in AR

- Associated coronary artery disease
- Low aortic diastolic pressure leading to decreased myocardial perfusion (since coronary flow occurs mainly in diastole)
- Increased myocardial oxygen demand due to myocardial hypertrophy

Q. How do you differentiate between aortic regurgitation of rheumatic and syphilitic aetiology?

Rheumatic AR	Syphilitic AR
- Younger age group (10–40)	- Older age group (more than 40)
- Anginal pains less common	- Anginal pains more common (due to associated coronary artery involvement)
- Decompensation relatively late	- Decompensation relatively early
- EDM best heard at Erb's area	- EDM best heard at aortic area
- Soft, blowing character of EDM	- Cooing dove or seagull character of EDM
- Soft A_2 component	- Loud and tambour like A_2

Q. How will you clinically differentiate the early diastolic murmur of aortic regurgitation from that of pulmonary regurgitation?

Aortic regurgitation murmur	Pulmonary regurgitation murmur
• Best heard at Erb's area or aortic area • Better heard during expiration • Begins just after A_2 • Decreases with amyl nitrite inhalation • Increases with hand grip and IV phenylephrine	• Best heard at pulmonary area • Better heard during inspiration • Begins just after P_2

Q. What is meant by Austin Flint murmur (AFM)?

- Mid-diastolic, low-pitched, rumbling murmur heard at the apex in severe AR
- Resembles mitral stenotic murmur
- Best heard at apex using diaphragm of stethoscope with patient in left lateral position

Possible Mechanisms

- Diastolic mitral regurgitation
- Relative mitral stenosis due to aortic regurgitant jet pushing the anterior mitral leaflet upwards, thus impeding the flow of blood from left atrium
- Low-pitched vibrations of the AR murmur itself being heard at the apex due to acoustical filtering properties of chest.
- Turbulence generated by the mixing of antegrade mitral flow stream with retrograde aortic flow within the left ventricular cavity.

Q. How will you clinically differentiate Austin Flint murmur from the murmur of mitral stenosis (MS)?

Feature	AFM	MS
• Diastolic thrill	–	+
• Loud first heart sound (S_1)	–	+
• Third heart sound (S_3)	+	–
• Opening snap (OS)	–	+
• Evidence of pulmonary hypertension	–	+
• Evidence of RV enlargement and/or hypertrophy	–	+
• Evidence of LV enlargement and/or hypertrophy	+	–
• Presystolic accentuation	±	+
• Murmur decreases with amyl nitrite	+	–
• Atrial fibrillation	–	+

Q. Discuss the aetiology, clinical features and management of tricuspid stenosis (TS).

- Aetiology
  - Rheumatic (usually associated with mitral and aortic valve disease)
  - Carcinoid syndrome
  - Congenital
- Clinical features
  - Clinical manifestations of associated mitral stenosis may dominate
  - Little or no dyspnoea
  - Fatigue is common
  - Refractory oedema, ascites and marked hepatomegaly with presystolic pulsation
  - JVP is raised with prominent *a* waves (giant *a* waves) and slow *x* descent
  - At lower-left sternal border, a tricuspid opening snap (OS), loud first heart sound and a mid-diastolic murmur with presystolic accentuation are heard
  - Tricuspid murmur increases during inspiration (**De-Carvallo's sign**)

- Treatment
  - Salt and fluid restriction
  - Diuretics
  - Surgical relief of tricuspid stenosis

Q. Discuss the aetiology, clinical features and management of tricuspid regurgitation.

Q. What is De-Carvallo's sign?

- Aetiology
  - Functional tricuspid regurgitation (most common)—rheumatic or congenital heart diseases with severe pulmonary hypertension, inferior wall infarction, cardiomyopathy and cor pulmonale.
  - Organic tricuspid regurgitation—rheumatic, Ebstein's anomaly, tricuspid valve prolapse, carcinoid syndrome, infective endocarditis, endomyocardial fibrosis, radiation therapy and trauma (e.g. endomyocardial biopsies, pacemaker lead placement).
- Clinical features
  - Symptoms of right ventricular failure become intensified.
  - Oedema, ascites and pleural effusion.
  - Hepatomegaly with systolic pulsations.
  - JVP is raised with prominent v waves and rapid y descent.
  - A blowing pansystolic murmur at the lower-left sternal border, which is intensified during inspiration and reduced during expiration (De-Carvallo's sign).
- Treatment
  - Treatment of underlying heart disease reduces functional tricuspid regurgitation.
  - Surgical treatment of tricuspid regurgitation consists of tricuspid valve replacement or repair of the annulus.
  - In those undergoing left-sided valve surgery, tricuspid valve repair is universally recommended in the presence of severe coexistent TR.

Q. Discuss the clinical manifestations, investigations and management of pulmonary stenosis (PS).

- Majority are congenital and may be associated with maternal rubella syndrome (cataract, deafness, microcephaly, pulmonary artery stenosis or pulmonary valvular stenosis).
- May be an isolated lesion or associated with Fallot's tetralogy
- Rheumatic aetiology very uncommon
- May be supravalvular, valvular or infundibular
- Symptoms
  - Dyspnoea, fatigue
  - Central cyanosis, if right-to-left shunt develops (increased right ventricular pressure in congenital pulmonic stenosis may force open foramen ovale)
  - Angina or syncope indicates severe stenosis
- Physical findings
  - Prominent a waves on JVP
  - Increased right ventricular thrust in the form of left parasternal heave and epigastric pulsation
  - Systolic thrill, best felt with patient sitting up, leaning forwards and during inspiration
  - Wide splitting of second heart sound
  - Ejection click in valvular pulmonic stenosis. It is the only right-sided sound that is best heard during expiration and not accentuated with inspiration.
  - Ejection systolic murmur, best heard to the left of upper sternum, radiating to left shoulder and increasing with inspiration.
- Investigations
  - ECG shows right ventricular hypertrophy, and in severe cases, right atrial enlargement.
  - Chest radiography shows post-stenotic dilatation of pulmonary artery, characteristically extending into the left pulmonary artery branch.
  - Doppler echocardiographic study
  - Cardiac catheterisation

- Treatment
  - Mild-to-moderate stenosis requires no treatment except periodic evaluations.
    - Severe stenosis is treated by percutaneous pulmonary balloon valvotomy, surgical valvuloplasty or valve replacement.

Q. Discuss the manoeuvres useful in differentiating murmurs due to various cardiac diseases.

• **Valsalva**	During active strain phase against closed glottis, most murmurs reduce in intensity, except (a) murmur of hypertrophic cardiomyopathy (HCM) that gets louder and (b) murmur of mitral valve prolapse (MVP) that gets longer and louder
• **Respiration**	Right-sided sounds and murmurs get louder with inspiration except pulmonary ejection click
• **Handgrip**	By increasing afterload, handgrip augments murmur of mitral regurgitation (MR), aortic regurgitation (AR); does not affect murmur of aortic stenosis (AS) and decreases murmur of HCM and MVP
• **Squatting**	Causes a rapid increase in venous return and peripheral resistance thereby increases left ventricular volume. Murmurs of MR and AR get louder while that of HCM gets softer
• **Postextrasystolic beat**	Both HCM and AS murmurs get louder because of increased postextrasystolic contractility while MR murmur is unaffected

Q. Discuss the aetiology, pathology, clinical features, investigations, treatment and prophylaxis of infective endocarditis.

Q. Explain in brief about post-operative endocarditis.

- Infective endocarditis is due to microbial infection of the heart valve or the lining of cardiac chamber (endothelium).
- The causative organism could be bacterium, fungus or rickettsia.
- Streptococci and staphylococci account for the vast majority of cases.

Types of Infective Endocarditis

- Subacute endocarditis and acute endocarditis
- Native valve endocarditis and prosthetic valve or post-operative endocarditis
- Left-sided endocarditis and right-sided endocarditis

Note: Most physicians do not differentiate between subacute and acute infective endocarditis, and simply state them as infective endocarditis.

- Another classification of infective endocarditis is left-sided infective endocarditis, left-sided prosthetic infective endocarditis, right-sided infective endocarditis and device-related (permanent pacemaker, implantable cardioverter defibrillator) infective endocarditis.

Subacute Endocarditis

- Caused by organisms of relatively low virulence.
- Occurs on the damaged valves themselves or at sites, where the endothelium is damaged by a high pressure jet of blood (VSD, PDA, MR, AS, AR).
- Characterised by formation of vegetations, embolic episodes, mycotic aneurysms, valve regurgitation, splenic and renal infarcts, and immune glomerulonephritis.
- Common sources of infection are periodontal infections (dental treatment), gastrointestinal tract infections and urinary tract infections.

Acute Endocarditis

- A source of infection or portal of entry is often evident
- Caused by highly virulent and invasive organisms

- Can affect damaged valves as well as normal hearts
- Has a fulminant course, vegetations are more florid, valve destruction is greater and abscess (local and metastatic) formation is more common.

Post-Operative Endocarditis or Prosthetic Valve Endocarditis
- Follows cardiac surgery using prosthetic valves and other prosthetic materials.
- May occurs early (within 60 days of surgery) due to intraoperative or hospital-acquired infections, or late (after 1 year) due to infection with community-acquired organisms. Those occurring between 60 days and 1 year are a mixture of hospital-acquired episodes caused by less virulent organisms and community-acquired episodes.
- Aortic prosthetic valve more prone than mitral prosthetic valve.
- During first 3 months, after surgery mechanical heart valves are at higher risk for infection than are bio-prosthetic ones, but the rates of infection for the two valve types congregate later on and are comparable at 5 years.
- In early prosthetic valve endocarditis, *S. aureus* predominates followed by coagulase-negative staphylococci and fungi. After 2 months additional organisms include viridans streptococci and enterococci. In late endocarditis offending agents are the same with those causing native valve endocarditis.

Right-Sided Endocarditis
- Occurs in intravenous drug users
- Caused predominantly by organisms found on the skin (e.g. *Staphylococcus aureus*, *Candida*)
- Affects right-sided valves, particularly tricuspid valve
- May present with acute endocarditis

Predisposing Factors
- A variety of factors predispose to infective endocarditis. However, antibiotic prophylaxis is recommended only for a patient with a high risk of severe adverse outcome, should the patient develop endocarditis.

Cardiac Conditions Associated with the Highest Risk of Adverse Outcome from Endocarditis (Require Antibiotic Prophylaxis Before High-Risk Procedures)

- Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
- Previous infective endocarditis
- Congenital heart disease (CHD):
  - Unrepaired cyanotic CHD, including palliative shunts and conduits
  - Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after procedure
  - Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialisation)
- Cardiac transplantation recipients who develop cardiac valvulopathy

Procedures Associated with High Risk of Endocarditis

Procedures on respiratory tract
- Tonsillectomy and/or adenoidectomy
- Surgical operations (incision or biopsy) that involve respiratory mucosa
- An invasive respiratory tract procedure to treat an established infection (e.g. drainage of an abscess or empyema)

Procedures in oral cavity
- All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa (e.g. dental extractions, suture removal, placement of orthodontic band, root canal treatment, dental procedures with intraligamentous anaesthesia, and reimplantation of avulsed tooth)

Procedures on gastrointestinal tract
- None, unless procedure is done during an established infection

Procedures on genitourinary tract
- None, unless procedure is done during an established infection (e.g. cystoscopy during known enterococcal UTI)

Procedures on skin and musculoskeletal system
- None, unless procedure involves infected tissue

Note: Prophylaxis is no longer needed for routine anaesthetic injections through non-infected tissue, dental radiographs, placement of removable prosthodontic or orthodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of deciduous teeth, bleeding from trauma to the lips or oral mucosa, vaginal delivery, hysterectomy or tattooing. It is also not recommended for bronchoscopy, laryngoscopy, endotracheal intubation, cystoscopy, colonoscopy or skin suturing.

Common Organisms

Subacute endocarditis	Acute endocarditis	Post-operative endocarditis
• Viridans streptococci: • *S. sanguis* • *S. mitis* • *Streptococcus milleri* • *Streptococcus bovis* • *Enteroccocus faecalis* • *Staphylococcus aureus* • HACEK group*	• *Staphylococcus aureus* • *Pseudomonas* • *Candida* • *Streptococcus pneumoniae* • *Neisseria gonorrhoeae*	• *Staphylococcus albus* • *Candida* • *Aspergillus* • All organisms causing acute and subacute endocarditis

Haemophilus, Aggregatibacter (formerly Actinobacillus), Cardiobacterium, Eikenella and Kingella

- The commonest organism causing subacute endocarditis is *Streptococcus sanguis*. It is an α-haemolytic streptococcus belonging to *Streptococcus viridans* group. It is a normal inhabitant of oropharynx and gastrointestinal tract. *Streptococcus sanguis* is highly sensitive to penicillin.

Pathology and Pathogenesis

Endocardial Injury and Vegetation Formation

- The first step is endocardial injury, which may occur by many mechanisms. The most common mechanism is injury by turbulent blood flow from an acquired or congenital intracardiac abnormality. Alternatively, an intravascular catheter or other device may directly abrade endocardium. In injection drug users, direct injection of contaminating debris may damage tricuspid valve surface.
- The endothelial damage triggers sterile thrombus formation, which occurs by deposition of fibrin and platelets.
- Once a sterile thrombus is present, transient bacteraemia can seed the thrombus.
- Once bacteria have attached to the endocardium, additional deposition of fibrin and bacterial proliferation leads to mature vegetation formation.

Vegetations

- Vegetations are fibrin-platelet bacteria complexes.
- Vegetations have three layers, an inner layer of RBC, WBC and platelets, a middle layer of bacteria and an outer layer of fibrin.
- Vegetations are located differently on various valves.

- Mitral valve—atrial surface and line of apposition of valve cusps
- VSD—on the right ventricular endocardium and around the defect
- Aortic valve—on the ventricular surface
- PDA—on the pulmonary artery and ductus
- Chordae tendineae and papillary muscles may have vegetations and lead to rupture

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Embolisation

- Vegetations get detached and embolise
- Emboli may be septic or sterile
- Occur to kidney, spleen, brain and peripheral vascular system resulting in infarction
- Septic emboli cause arteritis with weakness of arterial wall resulting in mycotic aneurysms
- Brain abscess
- Pulmonary embolisation and infarction occur in VSD and PDA, and in right-sided endocarditis

Deposition of Immune Complexes

- Focal glomerulonephritis and microscopic haematuria
- Diffuse glomerulonephritis and renal failure
- Vasculitis of cerebral vessels leading to cerebrovascular accidents
- Perisplenitis

Clinical Features of Subacute Endocarditis

Features of Infection

- Vague symptoms like ill-health, fatigue, lassitude, loss of appetite, and loss of weight
- Low-grade or high-grade, intermittent or continuous fever with chills and rigors
- Clubbing in fingers
- Splenomegaly
- Brownish pigmentation of face and limbs called cafe au lait pigmentation

Features of Haemodynamic Changes

- Appearance of new murmurs, particularly a diastolic murmur
- Change in the character of an existing murmur
- Development of MR and TR due to rupture of papillary muscles or chordae tendineae
- Worsening of cardiac failure
- Acute left ventricular failure and pulmonary oedema due to rupture of valve cusps

Features of Embolism

- Cutaneous embolism—Janeway lesions on palms and soles
- Nails—splinter haemorrhages
- Spleen—painful splenomegaly
- Peripheral arteries—claudication, absence of peripheral pulses and gangrene
- Central nervous system—convulsions, hemiplegia, aphasia, loss of vision and cerebellar disturbances
- Kidneys—loin pain, haematuria and renal failure
- Lungs—pulmonary infarction, pleurisy and pleural effusion (right-sided endocarditis)

Features of Immunological Disturbances

- Osler's nodes—painful tender swollen nodules in pulps of fingers
- Roth's spots—circular retinal haemorrhages with white central spots
- Glomerulonephritis and haematuria

Clinical Features of Acute Endocarditis

- Severe, abrupt onset of febrile illness
- Prominent and changing heart murmurs
- Embolic episodes more common
- Rapid development of renal and cardiac failure

Clinical Features of Post-Operative Endocarditis

- Presents as an unexplained fever in a patient who has had cardiac valve surgery.
- Course depends on the virulence of the organism—prominent and changing heart murmurs, frequent embolic episodes, and rapid development of renal and cardiac failure.

Clinical Features of Right-Sided Endocarditis

- Pulmonary infarction, pleurisy and pleural effusion due to vegetation embolism
- Generally, has a favourable prognosis

Investigations

- Normocytic normochromic anaemia
- Leucocytosis
- Microscopic haematuria and albuminuria
- Raised ESR and CRP

- Blood culture—three specimens of 10 mL blood each are taken at intervals of 1 hour. Both aerobic and anaerobic cultures are done, rarely fungal culture also.

Negative Blood Cultures in Endocarditis

- Defined as endocarditis without aetiology following inoculation of at least three independent blood samples in a standard blood culture system with negative cultures after 7 days of incubation and subculturing.

- Prior antibiotic treatment (most common cause)
- Inadequate quantity of blood taken for culture
- Right-sided endocarditis
- Anaerobic infection
- Infection with fastidious organisms (e.g. *Haemophilus parainfluenzae, Brucella*)
- Fungal infections (*Candida, Histoplasma*)
- Noninfective endocarditis

- Serologic tests for Bartonella, C. burnetii, and Brucella in patients with negative blood cultures, who have risk factors for these infections.

Other Investigations

- Hyperglobulinaemia, positive rheumatoid factor, reduction in the complement levels and presence of circulating immune complexes.
- Echocardiography can detect the vegetations and identify the valve lesion, chamber dilatation and new prosthetic dehiscence. Transthoracic echocardiography has a sensitivity of about 75% for the diagnosis of vegetations. Transoesophageal echocardiography is mandatory, in cases of doubtful transthoracic examination, in prosthetic and pacemaker endocarditis or when an abscess is suspected.

Modified Duke Criteria for Infective Endocarditis

- Has a mean sensitivity of 80% for diagnosing infective endocarditis

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Major criteria
- Blood cultures positive
  - Typical microorganisms consistent with infective endocarditis from two blood cultures:
    - Viridans streptococci, *Streptococcus bovis*, HACEK group (*Heamophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella*), or
    - Community-acquired *Staphylococcus aureus* or enterococci in the absence of a primary focus

    OR
  - Other microorganisms consistent with IE from persistently positive blood cultures defined as:
    - Two positive cultures of blood samples drawn >12 hours apart, or
    - All of three or a majority of four separate cultures of blood (with first and last sample drawn 1 hour apart)

    OR
  - Single positive blood culture for *Coxiella burnetii* or positive serology for Q fever, *Bartonella* species and *Chlamydia psittaci*
- Evidence of endocardial involvement
  - Echocardiogram positive for IE:
    - Oscillating intracardiac mass without alternative explanation, or
    - Abscess, or
    - New partial dehiscence of prosthetic valve, or
    - New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)

Minor criteria
- Predisposition to infective endocarditis: Predisposing heart condition, injection drug use, previous infective endocarditis, or prosthetic valve or material
- Fever, temperature >38°C

- Vascular phenomena: Major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhages, subconjunctival petechiae, Janeway lesions
- Immunologic phenomena: Glomerulonephritis, Osler's nodes, Roth's spots, positive rheumatoid factor
- Microbiological evidence: Positive blood culture but does not meet a major criterion or serological evidence of active infection with organisms consistent with infective endocarditis

Pathological criteria
- Positive microbiology or histology of pathologic tissue material attained at surgery or autopsy (vegetations, valve tissue, embolic fragments or tissue/pus from intracardiac abscesses)

- Diagnosis of IE is definite in the presence of:
  - Pathological criteria, or
  - Two major criteria, or
  - One major and two minor criteria, or
  - Five minor criteria.
- Diagnosis of IE is possible in the presence of one major and one minor criteria, or three minor criteria.

Medical Treatment

Organism	Treatment
• Infective endocarditis awaiting culture report or culture negative	Benzylpenicillin plus gentamicin at the dose given below for 4–6 weeks. OR Ceftriaxone 2 g once a day for 4-6 weeks OR Amoxillin/clavulanate 12 g/day in four divided doses plus gentamicin 1.5 mg/kg twice a day for 4–6 weeks Vancomycin in penicillin-allergic patients
• Suspected staphylococcal endocarditis	Vancomycin 30 mg/kg/day in two divided doses (not to exceed 2 g/day) for 6 weeks and gentamicin 1 mg/kg three times a day for 1–2 weeks. Add rifampicin 20 mg/kg/day in two divided doses in prosthetic valve endocarditis
• Streptococci highly sensitive to penicillin	Benzylpenicillin 2–3 million units IV 4 hourly for 4 weeks OR Ceftriaxone 2 g IV once a day for 4 weeks OR Benzylpenicillin or ceftriaxone for 2 weeks plus gentamicin 3 mg/kg once a day for 2 weeks Vancomycin 30 mg/kg/day in two divided doses (not to exceed 2 g/day) for 4 weeks in penicillin-sensitive patients
• Streptococci less sensitive to penicillin	Benzylpenicillin (24 million units/day in six divided doses) or ceftriaxone for 4–6 weeks and gentamicin 3 mg/kg/day (as single infusion) for at least 2 weeks
• Anaerobic streptococci	Benzylpenicillin, metronidazole
• Staphylococcal endocarditis (methicillin-sensitive)	Cloxacillin 2 g 4 hourly or Cefazolin 2 g 8 hourly for 6 weeks PLUS gentamicin 1.5 mg/kg twice a day for 3–5 days
• Enterococcal endocarditis	Ampicillin 2 g 4 hourly or vancomycin plus gentamicin 1.5 mg/kg two times a day for 6 weeks
• Candida	Amphotericin

- In right-sided endocarditis due to *S. aureus* with pulmonary abscesses, daptomycin can be used.
- In case of infection of prosthetic valve the treatment should be continued for at least 6 weeks.

Surgical Treatment—Indications

- Progressive cardiac failure from valve damage.
- Endocarditis of prosthetic valve.
- Large vegetation (>10 mm) on a left-sided valve with an episode of embolisation, or very large (>15 mm) and mobile vegetation (high risk of embolism).
- Active infection persisting in spite of adequate treatment (when fever and bacteraemia are evident for more than 7–10 days despite adequate antibiotic treatment).
- Abscess formation, perivalvular involvement and fungal endocarditis are also considered indications for early surgery.

Infective Endocarditis Prophylaxis for Oral Procedures

Patient group	Antibiotic	Dose (single 30–60 minutes before procedure)
• Able to take oral medicine	Amoxycillin	2 g
• Unable to take oral medicine	Ampicillin, or	2 g IM/IV
	Cefazolin, or	1 g IM/IV
	Ceftriaxone	1 g IM/IV
• Allergic to penicillins or ampicillin and able to take oral medication	Cephalexin, or	2 g
	Clindamycin, or	600 mg
	Azithromycin/Clarithromycin	500 mg
• Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin, or	1 g
	Ceftriaxone, or	1 g
	Clindamycin	600 mg

Note: Cephalosporins should not be given to a patient who has a history of anaphylaxis, angio-oedema or urticaria with penicillins or ampicillin.

Infective Endocarditis Prophylaxis for Respiratory Tract Procedures

- As per information box for oral procedures.
- For patients, who undergo an invasive respiratory tract procedure to treat an established infection (e.g. drainage of an abscess or empyema), antibiotic regimen should contain an agent active against viridans streptococci. If such infection is known to be caused by *Staphylococcus aureus*, the regimen should contain an agent active against it, such as an antistaphylococcal penicillin or cephalosporin, or vancomycin (in patients allergic to β-lactams). Vancomycin should also be administered if the infection is known or suspected to be caused by a methicillin-resistant strain of *S. aureus*.

Infective Endocarditis Prophylaxis for Genitourinary and Gastrointestinal Tract Procedures

- Not recommended for patients who undergo genitourinary or gastrointestinal tract procedures including diagnostic oesophagogastroduodenoscopy or colonoscopy.
- Patients who have an established gastrointestinal or genitourinary tract infection or for those who receive antibiotic therapy to prevent wound infection or sepsis associated with a GI or GU tract procedure, it may be reasonable that the antibiotic regimen include an agent active against enterococci, such as penicillin, ampicillin, piperacillin or vancomycin.

Infective Endocarditis Prophylaxis for Skin and Soft Tissue Surgeries

- No prophylaxis indicated for routine surgeries.
- If a surgical procedure involves infected skin or musculoskeletal tissue the therapeutic regimen should contain an agent active against staphylococci and β-haemolytic streptococci, such as an antistaphylococcal penicillin or a cephalosporin. In case of allergy or suspected infection by methicillin-resistant strain of staphylococcus, vancomycin or clindamycin should be administered.

Q. Write a brief note on Osler's nodes.

- Result from vasculitis
- Small raised, painful, tender nodules of 0.5–1.5 cm diameter
- Seen on the pulps of fingers and toes, thenar and hypothenar eminences
- Last for 1–5 days
- Seen in infective endocarditis, SLE, gonococcal and typhoid infections

Q. Give a brief account of Janeway lesions.

- Subepithelial microabscesses
- Bacteria can be identified near but not in the lesion
- Seen in infective endocarditis
- Small, red, raised, painless lesions over the palms and soles

Q. Enumerate the important features of Roth's spots.

- Seen in infective endocarditis
- Due to immunological disturbances
- Elliptical or circular-shaped haemorrhagic areas with central white spots
- Seen on the retina by fundoscopy

Q. Briefly explain noninfective endocarditis.

- Refers to formation of sterile platelet and fibrin thrombi on cardiac valves and adjacent endocardium in response to trauma, circulating immune complexes, vasculitis or a hypercoagulable state.
- Symptoms are those of systemic arterial embolism.
- Diagnosis by echocardiography and negative blood cultures.
- Treatment consists of anticoagulants and treatment of underlying cause.
- Prognosis is generally poor, more because of the seriousness of predisposing disorders than the cardiac lesion.

Marantic Endocarditis

- Also known as non-bacterial thrombotic endocarditis.
- Thrombotic vegetations.
- Vegetations tend to form on congenitally abnormal cardiac valves or those damaged by rheumatic fever.
- Occurs in malignancy and wasting disorders.

Libman–Sacks Endocarditis

- Develops due to circulating immune complexes.
- Vegetations 3–4 mm in size.
- Vegetations composed of degenerating valve tissue.
- Most common on ventricular surface of mitral valve; aortic valve is rarely involved.
- May be clinically undetectable or become a nidus for infection (leading to infective endocarditis), produce emboli or impair valvular function.
- Seen in systemic lupus erythematosus.

Q. Discuss the aetiology and risk factors of ischaemic heart disease (IHD).

Q. Discuss pathogenesis of atherosclerosis.

Q. What is ankle-brachial index?

- Ischaemic heart disease (IHD) is a condition in which there is an imbalance between myocardial blood supply and its oxygen demand.

Aetiology

- Most coronary artery diseases are due to atheroma and its complications.
- Uncommon causes include severe aortic stenosis, congenital abnormalities of coronary arteries (aberrant origin of coronary arteries, myocardial bridging, etc.) and arteritis due to connective tissue disorders.

Pathogenesis of Atherosclerosis

- Initial lesions of atherosclerosis are fatty streaks.
  - Lipoprotein particles accumulate within intima.
  - Lipoprotein particles undergo oxidative modifications within fatty streaks.
  - Inflammatory cells infiltrate the early lesions of atherosclerosis. These cells include monocyte-derived macrophages and lymphocytes. Macrophages digest oxidised low-density lipoprotein that has also penetrated the arterial wall, transforming into foam cells and causing the formation of fatty streaks.
  - The activated macrophages release chemoattractants and cytokines that perpetuate the process by recruiting additional macrophages and vascular smooth muscle cells (which synthesise extracellular matrix components) at the site of the plaque.
- Not all fatty streaks progress to atheromas. Circulating monocytes may remove lipids from intima. High-density lipoprotein also mediates lipid removal from fatty streaks and atheroma. This reverse cholesterol transport by HDL explains its anti-atherogenic action. In addition, HDL maintains endothelial function and protects against thrombosis.
- Some lipid-laden foam cells die due to apoptosis (programmed cell death) which results in a lipid-rich, necrotic core.
- Fibrous tissue is formed around the lipid-laden macrophages. Smooth muscle cells synthesise fibrous tissue around the lipid core, resulting in formation of a fibrous plaque. There is also proliferation of smooth muscle cells in plaques.
- Endothelial dysfunction has been shown to be a major factor in initiation of atherosclerosis. It is associated with hypercholesterolaemia, diabetes, hypertension, cigarette smoking, etc.
- As plaques advance, they also accumulate calcium (calcification of plaque).
- Some plaques bulge into the lumen of the coronary artery and narrow it. This may lead to flow limitation, particularly during increased myocardial demand leading to ischaemic symptoms.
- Sometimes haemorrhage occurs into a plaque or its fibrous cap becomes cracked or partially detached. This flap may further narrow coronary lumen. The exposed thrombogenic material with the plaque may precipitate thrombosis, thus completely blocking the vessel lumen acutely and precipitating acute coronary syndromes.
- Characteristics of high-risk or vulnerable plaques include a large lipid core, thin fibrous caps, a high density of macrophages and T lymphocytes, a relative paucity of smooth muscle cells, and increase in plaque neovascularity and intraplaque haemorrhage.

Risk Factors

Modifiable (Modifiable by Lifestyle and/or Pharmacotherapy)

- Smoking
  - There is a dose linked relationship between smoking and IHD.
  - The relative risk of death from IHD for smokers compared to non-smokers is highest in the young and less in older people.
- Cholesterol
  - Hypercholesterolaemia (elevated LDL) predisposes to IHD. Lowering the high cholesterol concentration by diet or drugs reduces the risk of cardiac events.
  - Low HDL cholesterol (<40 mg/dL).

Note: HDL ≥60 mg/dL is a "negative" risk factor, i.e. it protects a person from IHD. Blood levels of HDL vary inversely with those of triglycerides. Independent role of triglycerides in IHD is controversial.

- Arterial hypertension
  - Blood pressure ≥140/90 mmHg or on antihypertensive medications.
  - Even mild arterial hypertension is risk factor for IHD.
- Diabetes mellitus
  - Associated with diffuse coronary atheroma and IHD.
  - Insulin resistance (metabolic syndrome) may be associated with lipoprotein abnormalities (diabetic dyslipidaemia) that include small, dense LDL particles, low HDL and elevated triglycerides, all of which may increase IHD risk.

- Physical inactivity
- Dietary factors
  - Diets deficient in polyunsaturated fatty acids (PUFA).
  - Low vitamin C and vitamin E.
- Coagulation factors
  - Fibrinogen and factor VII are associated with increased risk of myocardial infarction.
- Obesity
  - Obesity (BMI $\geq$ 30 kg/m^2) predisposes to IHD.
- Stress factors
  - Occupations and events of stressful nature are risk factors for IHD.

Non-Modifiable

- Geographical influences
  - In some countries the incidence of IHD is increasing, whereas in other countries it is declining.
- Family history of premature CAD:
  - At the age of < 55 years in males.
  - At the age of < 65 years in females.
- Age
  - Men $\geq$45 years.
  - Females $\geq$55 years (post-menopausal).
- Genetic factors
  - 40% of the risk of developing IHD is controlled by genetic factors.
  - Genetic factors operate in hyperlipidaemia, plasma fibrinogen concentration and other coagulation factors, some of which can be modified using lifestyle changes.

Emerging Risk Factors (Remain Controversial)

- Apolipoprotein B
- Lipoprotein(a) [Lp(a)]
- C-reactive protein (high sensitivity)
- Hyperhomocysteinaemia
- Infection
- Small and dense LDL particles
- Impaired fasting glucose

Ankle-Brachial Index (ABI)

- Ratio of systolic blood pressure at the ankle to systolic blood pressure at the brachial artery
- One of the most widely available markers of atherosclerosis and least expensive to perform.
- In the primary care setting, effectively used to assess cardiovascular risk and diagnose peripheral artery disease (PAD)
- An ABI $\leq$0.9 is the threshold for confirming lower-extremity PAD.
- An ABI $\leq$ 0.9 or $\geq$1.4 indicates increased risk of cardiovascular events and mortality, regardless of presence of PAD symptoms or other cardiovascular risk factors.

Q. Discuss the clinical manifestations, investigations and management of angina pectoris.

Q. Write a short note on angina decubitus, nocturnal angina, Prinzmetal's angina (variant angina) and microvascular angina.

Angina Pectoris

- A clinical syndrome of discomfort, due to transient myocardial ischaemia.
- Transient myocardial ischaemia is due to following:
  - Obstruction of coronary flow by atheroma
  - Coronary arterial spasm
  - Microvascular coronary dysfunction

- Angina is worsened by factors that increase myocardial oxygen requirement or reduce supply.

• Exercise	• Hyperthyroidism
• Anaemia	• Aortic stenosis
• Tachycardia	• Aortic regurgitation
• Hypertension	• Arrhythmias
• Emotional stress (anger, fright, stress)	• Cold wind

Pathophysiology

Myocardial Energy (Oxygen) Balance

- Myocardial ischaemia results from an imbalance between myocardial energy supply (oxygen and energy substrates like glucose and free fatty acids) and myocardial oxygen demand. Besides substrate supply, utilisation and enzymatic activities involved in metabolism may also play a role in the pathogenesis of myocardial ischaemia.
- Major determinants of myocardial oxygen demand are heart rate, blood pressure and myocardial wall tension (which is influenced by preload, afterload and contractility). Since myocardial oxygen extraction from coronary arterial blood flow at rest is normally high, changes in oxygen extraction cannot correct an imbalance. Any increase in myocardial oxygen needs is normally provided by rise in coronary blood flow.

Coronary Autoregulation

- Normally, ability of coronary arteries to increase blood flow to meet myocardial metabolic demand (coronary flow reserve) is about 4–6 times the resting value and occurs due to dilatation of coronary arteries.
- Coronary autoregulation is modified by atherosclerosis, ventricular hypertrophy, and alterations in autonomic nerve function and endothelial function.
- Up to 95% of coronary arterial resistance is accounted for by small intramural vessels that are not visualised during coronary angiography. About 5% of resistance arises within conductive epicardial coronary arteries.
- In patients with stable angina, a fixed reduction in the diameter of coronary arteries by at least 70% leads to reduction in coronary blood flow. Inability to increase oxygen extraction or coronary blood flow, together with elevated myocardial demand, leads to angina.

Clinical Features

History

- Pain is usually retrosternal in location and brought on by exertion. It is relieved by rest and sublingual nitrates. Pain seldom lasts more than 20 minutes. Character of the pain is squeezing, crushing, tightening, heaviness or aching. Pain commonly radiates to left arm, or less commonly to right arm, throat, back, chin and epigastrium. Often, the pain comes on while walking uphill after a heavy meal on a cold winter day. This defines chronic stable angina. Precipitating circumstances remain similar between episodes, thresholds may be predicted by patients and relief patterns become known. This type of angina occurs due to fixed stenosis of a coronary artery.
  - Angina severity is classified by New York Heart Association Classification into class I to class IV.
  - Many patients with angina also have silent episodes of angina, i.e. without any symptoms.
- Angina decubitus is pain while lying flat that raises end-diastolic left ventricular volume, myocardial wall tension and hence oxygen demand.
- Nocturnal angina is an unusual form of angina occurring in aortic regurgitation. It is characterised by paroxysmal, nocturnal anginal pains associated with nightmares, dyspnoea, palpitations, skin flushing, profuse sweating and wide pulse pressure. It does not respond to sublingual nitroglycerine. Nocturnal angina may also occur without associated AR and is due to respiratory pattern changes, episodic tachycardia, and hypoxia due to respiratory changes or recumbency.
- Prinzmetal's angina or variant angina or vasospastic angina is pain that comes capriciously due to coronary arterial spasm and is accompanied by transient ST segment elevation on ECG. It occurs at night, at rest or with exertion. Attacks can be precipitated by hyperventilation. Prognosis is generally better than those with fixed, significant obstructive lesions, although response to treatment may be poor to β-blockers. Calcium channel blockers are the main drugs used in this type of angina. β-blockers alone should not be used.
- "Microvascular" angina indicates angina-like pain, normal coronary angiograms and positive exercise tests, and occurs in patients with metabolic syndrome. It is more common in women. Response to nitrates is less reliable. β-blockers are more effective. Hormonal abnormalities, changes in pain perception with exaggerated sensitivity, insulin resistance

and psychological overlays may be factors related to this type of angina. Pathogenesis includes endothelial dysfunction, release of vasoactive substances, autonomic dysfunction, vascular smooth muscle dysfunction and loss of oestrogen. About 1% of patients die and 0.6% suffer a stroke within 1 year after their first hospital admission.

- Angina equivalents mean symptoms of myocardial ischaemia other than pain. These include dyspnoea, faintness, fatigue and eructations precipitated by exertion and relieved with rest. At times, there may be no symptoms (silent angina). Angina equivalents and silent angina are more common in women, elderly and diabetics.

Physical Examination

- Usually negative, but may find tendon xanthomas, thickening of Achilles tendons, arcus lipoidosis in a young patient, aortic valve disease, diabetes, peripheral vascular disease, thyroid disease or obesity.
- The following physical signs are those of "myocardial ischaemia". The presence of one or more of them during an attack of pain may be suggestive.

• Rise in blood pressure and heart rate	• Dyskinetic segment around the apex
• Fourth heart sound	• Paradoxical splitting of second heart sound
• Murmur of mitral regurgitation due to papillary muscle dysfunction	• Relief of pain by carotid sinus massage (Levine test)

Investigations

- Electrocardiography—ECG is normal in most patients at rest and in between attacks. Most convincing evidence is demonstration of reversible ST segment depression or elevation, with or without T wave inversion during an attack of pain. Patient may require exercise testing, e.g. treadmill testing or bicycle ergometry.
- Stress myocardial perfusion scanning using radioactive thallium (^{201}thallium) or technetium (^{99m}technetium-sestamibi). If a patient cannot perform exercise, pharmacological challenge is performed using dipyridamole, adenosine or dobutamine. Dipyridamole and adenosine raise blood flow in healthy coronary arteries, stealing blood from myocardium served by obstructed vessels. Dobutamine raises myocardial oxygen demand and is useful in patients who cannot raise their heart rates adequately during exercise.
- Echocardiography (including stress echocardiography) and radionuclide blood-pool scanning provide information about ventricular function.
- Coronary arteriography provides detailed information about the extent and site of coronary artery stenosis.

Indications for Coronary Angiography

• Markedly positive stress test	• Prior revascularisation procedure
• Strong indication for left main coronary artery or three vessel disease	• Indeterminate stress tests but clinical features of IHD
• Nonatherosclerotic cause of ischaemia (e.g. coronary arterial anomaly)	• Presence of heart failure
	• Unable to perform non-invasive tests
• Frequent readmissions for chest pain	• Occupation demands a definitive diagnosis
• Resistance to medical therapy	

- Newer modalities for diagnosing coronary artery disease include intravascular ultrasound, multiple-slice spiral computed tomographic coronary angiography (CTCA), magnetic resonance coronary angiography (MRCA) and positron emission tomography (which assesses myocardial viability using glucose metabolism).

Management

- Management of angina pectoris involves three phases:
  - Assessment of severity of symptoms and extent of the disease
  - Measures to control symptoms
  - Measures to improve life expectancy
- The management of angina pectoris can be discussed under three headings:
  - General measures
  - Drug treatment
  - Surgical treatment

General Measures

- Proper explanation about the disease.
- Avoid walking after meals, particularly in cold, against a wind.
- Avoid unaccustomed strenuous exercises, stop smoking and reduce weight.
- Hyperlipidaemia treated with diet and drugs (with the goal of reducing LDL <100 mg/dL; goal of <70 mg/dL in very high-risk patients).
- Control of hypertension and diabetes (ACE inhibitors are useful in these patients).
- Correction of precipitating conditions such as anaemia, valvular disease and arrhythmias.

Drug Treatment

- Following groups of drugs are used in the management of angina pectoris:
  - Nitrates
  - β-adreno receptor antagonists (β-blockers)
  - Calcium antagonists
  - Platelet inhibitors
  - Miscellaneous (ranolazine, trimetazidine, nicorandil, and ivabradine)

Nitrates

- GTN acts by venous and arteriolar dilatation, which lowers blood pressure, reduces venous return to heart and dilates coronary vessels. By producing venodilation, end-diastolic volume and pressure is reduced, leading to increased subendocardial perfusion.
- Fresh glyceryl trinitrate (500 μg) sublingually relieves pain in 2–3 minutes and produces mild headache. Patient is instructed to spit out or swallow the tablet once pain is relieved.
- Best use of GTN is prophylactically before exercise known as liable to produce pain.
- Not more than two tablets per hour should be used. Use of GTN should be encouraged because physical activity promotes the formation of collateral vessels. GTN can be given sublingually, percutaneously as paste or patch, and slow-release buccal tablet. GTN is virtually ineffective when swallowed. It deteriorates on exposure to air, light and moisture.
- Isosorbide dinitrate has prolonged action (10–20 mg two to three times a day) and is given by mouth. Headache is a common side effect. Tolerance develops and dose needs to be increased. It is important to have a 10- to 12-hour nitrate-free period to avoid tolerance. Hence, doses are given in the morning and afternoon. Patients using patches must remember to remove them at night to avoid development of tolerance.
- Isosorbide mononitrate needs to be given once or twice a day.
- Long-acting nitrates are often used if symptoms are not controlled with β-blockers and/or calcium channel blockers. Although there is no evidence that nitrates improve patient prognosis, long-acting nitrates reduce the frequency and severity of angina attacks in patients with stable angina.
- Phosphodiesterase inhibitors (type 5 or PDE5), such as sildenafil, tadalafil and vardenafil, must not be used with nitrates within the same 24-hour period because of risk of severe hypotension.
- Other contraindications to nitrate use include obstructive hypertrophic cardiomyopathy, severe aortic stenosis, constrictive pericarditis, mitral stenosis, and closed-angle glaucoma.

β-blockers

- They reduce myocardial oxygen demand by reducing heart rate for a given level of exercise, reducing heart rate response to anxiety and reducing myocardial contractility. In addition, because of their negative chronotropic effect β-blockers prolong diastole, raising coronary artery blood flow and myocardial perfusion.
- Propranolol is started in a small initial dose (20 mg thrice daily) and gradually increased to 80–120 mg thrice daily.
- Cardioselective β-blockers have fewer peripheral side effects. These include metoprolol (50–200 mg/day) and atenolol (50–200 mg/day).
- Carvedilol (3.125–25 mg twice a day) has additional unique effects that include its antiarrhythmic effects, antioxidant and antiproliferative properties that inhibit apoptosis.
- β-blockers should not be withdrawn abruptly, as there is the risk of dangerous arrhythmias and myocardial infarction. This occurs due to upregulation of β-adrenergic receptors when patients are treated with β-blockers.
- Absolute contraindications to β-blockers are severe bradycardia, conduction system disease (sinus node dysfunction and/or high-grade AV block), asthma, peripheral vascular disease, depression and overt heart failure.
- Prinzmetal's angina may worsen with β-blockers due to an unopposed α-adrenergic effect.

- Patients with cocaine-induced coronary vasoconstriction may develop severe hypertension and seizures when given β-blockers.

Calcium Antagonists

- They inhibit the slow inward current caused by the entry of extracellular calcium through cell membrane of excited cells, particularly arteriolar smooth muscle and cardiac atrial cells. In arterioles, it results in vasodilatation and hence reduces blood pressure. In cardiac muscle it reduces inotropy and conductivity. Dilatation of peripheral arteries reduced blood pressure (afterload) thereby reducing myocardial wall tension and hence myocardial oxygen consumption.
- Dihydropyridine calcium channel blockers (amlodipine, nifedipine, felodipine and nicardipine) produce coronary and peripheral arterial dilatation, and negative inotropy while nondihydropyridine calcium channel blockers (verapamil, diltiazem) in addition reduce conductivity.
- Nifedipine is a powerful coronary and systemic arteriolar dilator. This can provoke reflex tachycardia. Only long-acting preparations are recommended at present, usually along with a β-blocker. Short-acting nifedipine can increase mortality due to myocardial infarction.
- Verapamil is given at a dose of 40–80 mg thrice daily. Common side effect is constipation. It has a negative inotropic effect and should be avoided in patients with impaired ventricular function.
- Both verapamil and diltiazem are contraindicated in patients with uncompensated heart failure because of their negative inotropic effects.
- Since β-blockers have been shown to reduce mortality after myocardial infarction, it is reasonable to start a β-blocker and then add a calcium channel blocker if required. However, β-blockers should not be combined with verapamil as both have synergistic effect on rate and myocardial contractility.
- Calcium blockers are indicated in the following situations:
  - Response to β-blockers inadequate
  - History of asthma or chronic obstructive airway disease, or peripheral vascular disease where β-blockers should be avoided
  - Sick-sinus syndrome or significant atrioventricular blocks.
  - Prinzmetal's angina
  - Adverse effects to β-blockers

Antiplatelet Agents

Aspirin

- The antianginal drugs discussed above have been shown to ameliorate symptoms only; they may not reduce mortality.
- Aspirin (and lipid-lowering agents) have been shown to improve survival.
- Inhibits the synthesis of prostaglandins, notably thromboxane A_2, a potent vasoconstrictor and platelet activator.
- Dose is 75–150 mg/day.

P2Y$_{12}$ antagonists

- Clopidogrel is a platelet inhibitor that is useful in patients who cannot tolerate aspirin.
- It may have a synergistic effect when combined with aspirin in patients following acute coronary syndrome or implantation of a drug-eluting stent; benefit of combination has not been shown in chronic stable angina.
- Prasugrel and ticagrelor are new P2Y$_{12}$ antagonists that achieve greater platelet inhibition, compared with clopidogrel.

Miscellaneous Drugs

Angiotensin Converting Enzyme Inhibitors

- These agents reduce total mortality, MI, stroke and heart failure among specific subgroups of patients, including those with heart failure, chronic kidney disease, hypertension and diabetes.

Ranolazine

- Ranolazine is a late sodium ion channel inhibitor. By preventing intracellular sodium overload, calcium accumulation is thwarted, diastolic muscle relaxation is normalised, and myocardial oxygen balance and myocardial blood perfusion are preserved.
- It exerts its antianginal effect without affecting heart rate and blood pressure, making it an ideal drug of choice in bradycardic and hypotensive patients.
- Can be combined with other medications.
- Dose is 500–1000 mg twice a day.

Nicorandil
- It increases potassium ion conductance by opening ATP-sensitive potassium channels. It also produces smooth muscle-relaxation causing vasodilatation.
- Useful for associated protection of myocardium during ischaemia and prevention of intracellular calcium toxicity.
- Dose is 10–40 mg twice a day.

Ivabradine
- Selectively inhibits inward sodium-potassium current, an important pacemaking current in SA node cells. This slows the rate of diastolic depolarisation and lowers heart rate ("bradycardic" drug).
- Does not affect contractility, AV nodal conduction or haemodynamics.
- Can be combined with other agents.
- An important side effect is brightness in visual fields because the drug also blocks the retinal current. This side effect is often transient.

Trimetazidine
- A metabolic modulator that improves myocardial energetics at several levels, partially inhibiting oxidation of fats by decreasing activity of mitochondrial enzyme 3-ketoacyl coenzyme A thiolase (3-KAT). It increases myocardial glucose utilisation, prevents decrease in ATP levels in response to hypoxia or ischaemia, minimises free radical production and protects against intracellular calcium overload.
- It raises coronary flow reserve, lowers frequency of anginal episodes, improves exercise performance and spares the use of nitrates without changes in heart rate, negative inotropic or vasodilator actions.
- May be added to other drugs.

Surgical Treatment
- Percutaneous coronary interventions (PCI)—Percutaneous transluminal coronary angioplasty (PTCA) is the dilatation of coronary artery stenosis by a small balloon introduced percutaneously via an arterial catheter. Ideal for single-vessel coronary disease. Dilatation can be repeated if there is recurrence of symptoms. This is the treatment of choice for unstable angina (UA) when rest pain recurs despite full medical treatment. An advancement is the placement of a stent at the site of block that reduces the risk of reocclusion. These stents are of two types: Baremetal stents and drug-eluting stents. The latter stents are coated with drugs (e.g. sirolimus and paclitaxel) which may reduce the risk of reocclusion. Indications for PCI are:
    - Double vessel or triple vessel disease with out significant proximal left anterior descending arterial (LAD) lesions, with anatomy enabling catheter-based therapy and normal left ventricular failure.
    - Single vessel or double vessel disease without significant proximal LAD lesions, with high risk on non-invasive testing and a large area of viable myocardium.
    - Prior PCI with either recurrence of stenosis or high risk on non-invasive testing.
    - Failure of optimum medical therapy and with acceptable risk for PCI.
- Coronary artery bypass grafting (CABG)—Length of patient's saphenous vein is anastomosed to the aorta at one end and to a coronary vessel distal to a stenosis at the other. Ideal for left main coronary artery stenosis and significant stenosis in all three major coronary vessels. Alternatively, internal mammary artery can be used for grafting. Important indications of CABG are:
    - Significant left main coronary disease.
    - Triple vessel disease (particularly if left ventricular ejection fraction <50%).
    - Double vessel disease with significant proximal left anterior descending artery disease and either LVEF <50% or demonstrable ischaemic on non-invasive testing.
    - Failure of optimum medical therapy and with acceptable risk for CABG.

Q. What are acute coronary syndromes?
- Acute coronary syndrome refers to the constellation of symptoms manifesting as a result of acute myocardial ischaemia.
- It includes following conditions:
    - ST elevation myocardial infarction (STEMI).
        - Majority of patients with STEMI will develop Q wave MI (QwMI).
        - A small proportion of patients with STEMI and majority with NSTEMI will develop non-Q wave MI (NQwMI, previously called subendocardial infarction).
        - However, at present, the terms Q wave or non-Q wave infarctions are not used.

- Unstable angina includes patients with acute coronary syndrome with normal ECG and without positive cardiac injury markers in the blood.
- Non-ST segment elevation myocardial infarction (NSTEMI) is diagnosed when cardiac markers are elevated but there is no ST elevation in the ECG.
- · Since management of unstable angina and NSTEMI is similar, they are discussed together.
- Acute coronary syndromes as well as stable angina form parts of the spectrum of IHD, the most common cause being coronary artery disease (CAD).

Q. Discuss the clinical features, complications, investigations and management of acute myocardial infarction (ST elevation myocardial infarction—STEMI).

Q. Describe thrombolytic therapy in acute myocardial infarction.

Acute Myocardial Infarction

- Myocardial infarction is myocardial necrosis occurring as a result of a critical imbalance between coronary blood supply and myocardial demand. It is usually due to the formation of an occlusive thrombus at the site of rupture of an atheromatous plaque in a coronary artery.
- In young patients, a hypercoagulable state may result in acute myocardial infarction.
- Another important cause of myocardial infarction is the use of cocaine. Cocaine use results in acute MI by various mechanisms including coronary vasospasm and hypercoagulability in the background of heightened sympathetic activity. Long-term cocaine use also results in hastened atherosclerosis.
- ST-segment is persistently elevated in STEMI.
- Subendocardial infarct is an infarct confined to subendocardial region. Transmural infarct is an infarct involving the full thickness of myocardium. However, these terms are no longer used at present (see acute coronary syndromes).
- Silent infarct is characterised by no symptoms but only ECG changes.

Clinical Features

Symptoms

- Cardinal symptom is chest pain, but breathlessness, syncope, vomiting and extreme tiredness are common. Pain is at the same site as for angina, but is more severe and prolonged. It is severe, with pallor and a peculiar facial expression. Pain is described as tightness, heaviness or constriction.
- Pain may be absent in patients with prior heart failure, prior stroke, age >75 years, and diabetes mellitus. Painless MI also more common in females compared to males.

Signs

• Mild fever	• Diffuse apical impulse
• Pallor, sweating	• Soft first heart sound
• Tachycardia or bradycardia	• Third heart sound
• Arrhythmias	• Pericardial friction rub
• Narrow pulse pressure	• Systolic murmur due to mitral regurgitation or uncommonly due to VSD
• Raised JVP	• Basal crepitations

Note: A small proportion of patients with acute MI or unstable angina have their pain partially or fully reproduced on chest wall palpation. Hence, local chest wall tenderness should not be used as a criterion to exclude acute coronary syndrome.

Complications

Arrhythmias

• Sinus bradycardia	• Atrial tachycardia
• Sinus tachycardia	• Atrial fibrillation
• Ventricular ectopic beats	• Ventricular fibrillation
• Ventricular tachycardia	• Heart blocks
• Accelerated idioventricular rhythm	

Cardiogenic Shock

- May be caused by an arrhythmia; its correction would bring about dramatic relief.
- Hypovolaemia due to excessive diuretic therapy or recurrent vomiting is another cause.
- If none of these is responsible, cardiogenic shock usually reflects extensive myocardial damage and indicates a bad prognosis.
- Risk factors for development of cardiogenic shock include older age, anterior MI, hypertension, diabetes mellitus, multivessel coronary artery disease, prior MI or angina, prior diagnosis of heart failure, STEMI and left bundle branch block.

Other Complications

- Cardiac failure, most commonly manifesting as pulmonary oedema
- Infarction of the mitral papillary muscle leading to mitral regurgitation and pulmonary oedema
- Rupture of interventricular septum leading to a murmur of VSD and severe hypotension
- Cardiac tamponade due to rupture of ventricle into pericardial sac
- Cerebral and peripheral embolism resulting from the detachment of a ventricular mural thrombus
- Deep vein thrombosis and pulmonary embolism in patients on prolonged bed rest
- Ventricular aneurysm and dyskinetic or akinetic segments
- Dressler's syndrome is otherwise known as post-myocardial infarction syndrome. It is an autoimmune reaction to necrotic muscle. Syndrome is characterised by fever, pericarditis and pleurisy. Occurs a few weeks or even months after the infarction. Treatment is with aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids.

Investigations

Electrocardiogram

- Should be done and interpreted within 10 minutes of arrival.
- ECG is useful in confirming the diagnosis. The typical changes are seen in leads facing the infarcted area (e.g. antero-septal, anterolateral, strict anterior, inferior and posterior wall infarction). These changes include:
  - ST segment elevation (with reciprocal depression in the opposite leads) ≥ 2 mm in men and 1.5 mm in women in leads V_2–V_3 or ≥ 1 mm in other contiguous chest or limb leads in the absence of left ventricular hypertrophy or left bundle branch block.
  - Appearance of a new left bundle branch block also indicates acute infarction and qualifies for reperfusion therapy.
  - Appearance of pathologic Q waves, i.e. initial negative deflections of 0.04 seconds or more in leads other than aVR and V_1.
  - In very early MI, the T waves may become tall and peaked (hyperacute myocardial infarction). These are transient and last for a few hours only.
  - ST depression in ≥ 2 precordial leads (V_1–V_4) may indicate STEMI of posterior wall.
  - Multilead ST depression with coexistent ST elevation in lead aVR indicates left main or proximal left anterior descending artery occlusion.

ECG and Location of MI

- Inferior wall MI—changes in leads II, II, aVF
- Anterior wall MI—changes in leads V_1 to V_6, I and aVL
- Anteroseptal MI—changes in leads V_1 to V_2
- Anterolateral MI—changes in leads V_4 to V_6, I and aVL
- Posterior wall MI—tall R and ST depression in leads V_1 and V_2
- Right ventricular infarction—changes in V_4R

Plasma Enzymes (Cardiac Injury Enzymes)

1. Creatine kinase (CK)
2. Aspartate aminotransferase (AST)
3. Lactate dehydrogenase (LDH)
4. Myoglobin
5. Troponins (troponin I and troponin T)

- CK starts to rise at 4–6 hours, peaks by about 12 hours and falls to normal in 48–72 hours. Measurement of the myocardial isoenzymes of CK (CK-MB) is more specific for myocardial infarction. Total CK is also elevated in skeletal muscle diseases (e.g. polymyositis, and muscular dystrophies), cardioversion, skeletal muscle damage, hypothyroidism and stroke.
- AST starts to rise by about 12 hours and reaches a peak on the 1st or 2nd day.
- LDH starts to rise after 12 hours, reaches a peak after 2–3 days and may remain elevated for a week. A rise in the level of LDH_1 (an isoenzyme of LDH) is a more sensitive indicator of myocardial infarction than total LDH.
- Myoglobin is increased within 2–6 hours of onset of symptoms and remains elevated for 7–12 hours.
- Cardiac troponins include cardiac troponin T (cTnT) and cardiac troponin I (cTnI). The sensitivity of troponins is similar to that of CK-MB. However, cTn remains elevated for 100–200 hours after acute MI and therefore, this assay may have particular utility in the evaluation of patients who present sufficiently long after their episode of chest pain. Further, nearly one-third of patients with label of unstable angina also have elevated cTn, which classifies these group of patients to non-ST elevation MI.
  - Other conditions that may produce elevation of troponins include sepsis, hypotension, atrial fibrillation, intracranial haemorrhage, cardiac contusion, cardioversion, myocarditis, pulmonary embolism and chronic renal failure.

Changes in plasma enzyme concentrations after myocardial infarction
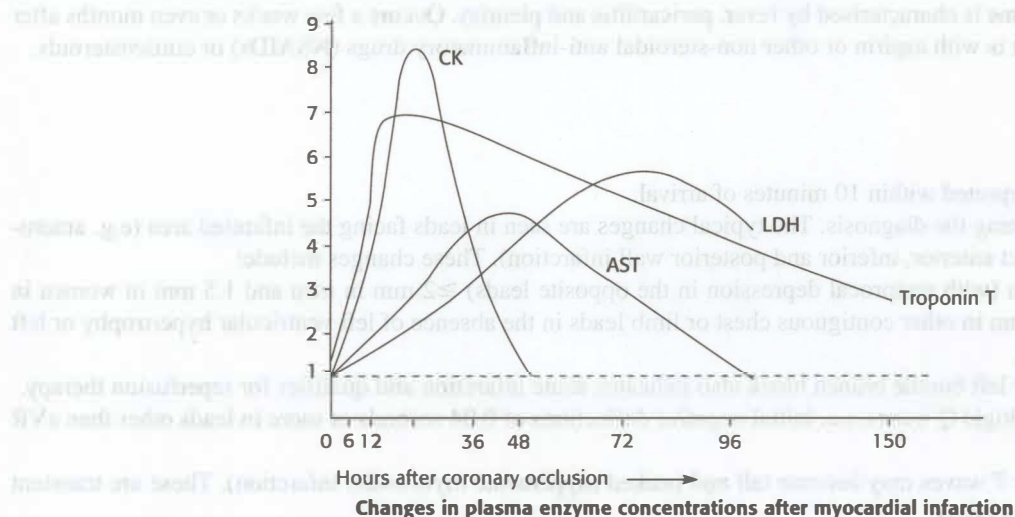
Note: CK and troponins are the first to rise, followed by AST and then LDH.

Other Investigations

- Leucocytosis with a peak on 1st day.
- Raised ESR that may remain so for days.
- Elevated C-reactive protein.
- Chest radiography.
  - Heart size is usually normal. Enlargement of cardiac shadow may indicate previous myocardial damage or pericardial effusion.
  - Evidence of pulmonary oedema.
- Radionuclide scanning shows the site of necrosis and the extent of impairment of ventricular function.
- Echocardiography for regional wall motion abnormality and ejection fraction.

Management

- In the first 24–48 hours when the risk of fatal arrhythmia is highest, the patients are best treated in an intensive coronary care unit.

Management of Acute Myocardial Infarction

Initial treatment
- Attach a cardiac monitor
- Secure an intravenous line
- Administer oxygen if oxygen saturation <94%
- Administer sublingual nitrate (if not taken by the patient and pain is present)
- If no relief, give intravenous morphine 3–5 mg along with an antiemetic. May repeat it 5–10 minutes after the first dose
- Give aspirin 150 mg to be chewed
- Give clopidogrel 300–600 mg orally (unless coronary artery bypass surgery is contemplated)

Confirm diagnosis
- ECG
- If available, troponin T or I and CK-MB

Specific therapy
- Thrombolysis or percutaneous coronary interventions
- β-blockers unless contraindicated
- Treat complications (arrhythmias, congestive failure and shock)
- Admit in intensive coronary unit

Oxygen

- Hypoxaemia in patients with uncomplicated MI is usually caused by ventilation-perfusion abnormalities and may be exacerbated by CHF. Therefore, oxygen is administered to patients suspected of having an acute ischaemic syndrome and oxygen saturation <94%.

Nitrates

- Nitrates reduce oxygen demand and myocardial wall stress by reducing both preload and afterload.
- If patient is stable, sublingual nitrate should be given.
- Intravenous nitroglycerine is recommended in patients with pump failure, pulmonary oedema, accelerated hypertension and continuing chest pain.

Control of Pain

- Morphine in a dose of 3–5 mg is administered intravenously every 10–15 minutes along with an antiemetic to control chest pain.
- The beneficial effects of morphine are mainly due to sedation and analgesia produced by it which result in reduction of myocardial oxygen demand. It also reduces preload to some extent which may be beneficial in patients with MI. β-blockers, nitroglycerine and thrombolysis may also help in relieving pain.

Antiplatelet Agents

- Early administration of aspirin to patients with acute MI has been shown to be of significant benefit in AMI. The patient is asked to chew 150 mg non-enteric-coated aspirin.
- Administer clopidogrel to all patients below the age of 75 years unless the need for coronary artery bypass surgery is likely.
  - If PCI is planned, loading dose is 600 mg
  - If fibriniolysis is planned, loading dose is 300 mg if age <75 years; patients above 75 years should receive 75 mg/day without loading dose.
  - It should be continued for at least 14 days, although it is reasonable to continue for 1 year, particularly after stent placement.
- Prasugrel is another orally administered P2Y$_{12}$ receptor antagonist that is more potent, more rapid in onset and more consistent in its inhibition of platelet aggregation than are currently approved doses of clopidogrel. However, there is increased risk of bleeding in patients with a history of transient ischaemic attack or stroke; those above 75 years of age or those who weigh <60 kg do not benefit from it. It is given in a loading dose of 60 mg followed by 10 mg/day.
- Third P2Y$_{12}$ receptor antagonist is ticagrelor which is given in a loading dose of 180 mg followed by 90 mg twice a day.

β-Blockers

- These agents decrease oxygen demand by lowering the heart rate and blood pressure. They also counter the direct adverse effects of catecholamines and have antiarrhythmic properties. These agents are also useful to control tachycardia, hypertension and continued angina.
- Contraindications to the use of β-blockers include bradycardia (rate <60/minute), systolic blood pressure of less than 100 mmHg, moderate-to-severe congestive heart failure, AV conduction defects and severe obstructive lung disease.
- β-blockers given orally or intravenously (if patient has hypertension, tachycardia or continuing chest pain) within first few hours of infarction are useful in reducing mortality. The commonly used β-blockers include metoprolol and esmolol.

Calcium Channel Blockers

- These agents are not recommended in the management of AMI. However, it is reasonable to give verapamil or diltiazem to patients with STEMI for whom β-blockers are ineffective or contraindicated for relief of ongoing ischaemia or control of a rapid ventricular response (with atrial fibrillation or atrial flutter) in the absence of CHF, LV dysfunction or atrioventricular block.
- Short-acting nifedipine is contraindicated in these patients.

Angiotensin-Converting-Enzyme Inhibitors

- Angiotensin-converting-enzyme (ACE) inhibitors improve the myocardial function by reducing myocardial remodelling.
- ACE inhibitors are recommended within 24 hours in all patients with STEMI with anterior location, heart failure, or ejection fraction ≤40%. Initiate the treatment with short-acting ACE inhibitor, captopril, in a dose of 12.5 mg. If the systolic pressure remains above 100 mmHg, increase the dose to 25 mg 8 hourly with a constant watch on blood pressure. If patient is intolerant to ACE inhibitors, angiotensin receptor blocking agents may be given.

Statins

- Intensive statin treatment (e.g. atorvastatin 40–80 mg) should be considered as early as possible, but within 24 hours after hospital admission in patients presenting with STEMI.
- Pre-existing statin therapy should be continued in patients presenting with STEMI.
- Besides lowering cholesterol, beneficial effects are also related to direct effects on endothelial function, oxidative stress, inflammation, thrombosis as well as plaque stabilisation.

Thrombolytic (or Fibrinolytic) Therapy

- The goal is to initiate fibrinolytic therapy within 30 minutes (door-to-needle time or first medical contact-to-needle time).
- Thrombolytic agents: These include: streptokinase (STK); urokinase (UK); recombinant plasminogen activator (rt-PA, alteplase), reteplase, tenecteplase, anisoylated plasminogen streptokinase activator complex (APSAC, and anistreplase) and single-chain urokinase plasminogen activator (scu-PA). All these agents act as direct or indirect plasminogen activators leading to generation of plasmin that lyses the clot. rt-PA, reteplase, tenecteplase and scu-PA do this only at the site of clot (fibrin-specific fibrinolytics) whereas others generate plasmin in the systemic circulation leading to a systemic lytic state that leads to a reduction in blood viscosity, and exerts strong anticoagulant and antiplatelet effects.
- Fibrin-specific fibrinolytic agents have been shown to reduce mortality compared with STK.
- Fibrin-specific fibrinolytics also lack the significant acute side effects of hypotension and allergy caused by STK.
- STK may be associated with a lower incidence of intracranial haemorrhage, particularly in older people, but the overall mortality is still lower with the use of fibrin-specific fibrinolytic agents.
- Thrombolytic therapy is not recommended at present for patients with NSTEMI and unstable angina.

Indications for Thrombolysis in Acute Myocardial Infarction

Thrombolysis shown to be of definite value
- ST segment elevation of greater than 0.1 mV in two or more contiguous leads, with time to therapy 12 hours or less
- Bundle-branch block (obscuring ST segment analysis) and history suggestive of acute MI for less than 12 hours

Thrombolysis may be of some benefit
- ST segment elevation with time to therapy 12–24 hours if there is clinical and/or ECG evidence of ongoing ischaemia or haemodynamic instability provided PCI is not available.

Thrombolysis not indicated/may be harmful
- ST segment depression only (unless leads V₁–V₄ show ST depression related to posterior wall MI)
- Time to therapy >24 hours

- STK is used in a dose of 1.5 million units intravenously as an infusion over a period of 1 hour.
- In patients >65 kg, rt-PA (alteplase) is given in a dose of 15 mg bolus followed by 50 mg over 30 minutes and 35 mg over the next 60 minutes. For patients <65 kg, dose is 15 mg bolus; then 0.75 mg/kg over 30 minutes and 0.5 mg/kg over the next 60 minutes.
- Signs of re-perfusion:
  - Sudden relief of chest pain.
  - Reduction by 50% of the initial ST-segment elevation within 60–90 minutes of fibrinolytic therapy.
  - Onset of re-perfusion arrhythmias (mainly accelerated idioventricular rhythm and frequent ventricular ectopics).
  - Early peaking of CK-MB enzyme.
- Complications:
  - The major complication of thrombolytic therapy is haemorrhage that occurs in about 30% of cases.
  - The most common site of haemorrhage is from puncture sites and genitourinary system.
  - Intracranial haemorrhage occurs in about 0.5% of cases.
  - Use of STK and APSAC may be associated with allergic reactions.
  - Hypotension may occur if STK is infused rapidly.

Contraindications to Thrombolytic Therapy

Major contraindications	Other contraindications
- Active bleeding (except menses) - Severe uncontrolled hypertension - History of haemorrhagic stroke - Ischaemic stroke within 3 month (except for acute ischaemic stroke within 3--4.5 hours) - Suspected aortic dissection - Known intracranial aneurysm or AV malformation - Known intracranial neoplasm (primary or metastatic) - Intracranial/spinal surgery within last 3 months - Significant cranial/spinal trauma in last 3 months	- History of poorly controlled severe hypertension - History of non-haemorrhagic stroke more than 3 months previously - Significant trauma within last 6 weeks - Traumatic or prolonged (>10 minutes) cardiopulmonary resuscitation - For streptokinase (STK), previous exposure (>5 days previously) or previous allergic reaction - Major surgery within last 6 weeks - GI bleed within last 6 weeks - Pregnancy - Acute pericarditis

Antithrombin Therapy

- Antithrombin therapy in the form of heparin is required before the completion of infusion of rt-PA or tenecteplase. It is also recommended in patients receiving STK.
- Unfractionated heparin should be given as an initial bolus dose of 60 IU/kg (with a maximum dose of 4000 units) followed by an initial infusion of 12 IU/kg/hour (maximum 1000 units/hour), adjusted to attain the activated partial thromboplastin time at 1.5–2 times control.
- Low-molecular weight heparin as an adjunct to thrombolytics may result in higher re-perfusion rate and lower re-occlusion rate compared to unfractionated heparin.
- Direct thrombin inhibitors (hirudin and bivalirudin) can be used as an alternative to heparin and Gp IIb/IIIa inhibitors in patients undergoing PCI.
- Another option is the use of fondaparinux unless PCI is planned when it should not be used as sole agent.
- These agents should be continued for at least 48 hours and preferably for 8 days.

Prophylactic Anticoagulants

- Use of low-dose heparin, i.e. 5000 units twice a day subcutaneously to prevent deep vein thrombosis and pulmonary embolism is indicated in those who do not receive fibrinolytic agents.

Percutaneous Coronary Interventions (PCI)

- These interventions include angioplasty (percutaneous transluminal coronary angioplasty—PTCA) or stent placement in the coronary artery. Stents may be bare metallic or drug-eluting, the latter containing sirolimus or paclitaxel. Though drug-eluting stents are considered to have lower risk of restenosis (by inhibiting intimal hyperplasia), recent data suggest both types of stents to be equally effective over long-term follow-up.
- Manual aspiration thrombectomy is reasonable for patients undergoing primary PCI before placing stents.

- PCI may be used solely in acute MI (primary PCI) or in combination with thrombolytic therapy when thrombolysis fails (rescue PCI).
- It can also be given following thrombolysis (facilitated PCI). However, this type of re-perfusion may be inferior to thrombolysis alone or primary PCI.
- Primary PCI is indicated in cardiogenic shock, acute severe heart failure and in presence of contraindications to thrombolytic therapy (irrespective of time delay from first medical contact).
- Glycoprotein IIb/IIIa inhibitors (abciximab and tirofiban) are often recommended in patients undergoing percutaneous interventions.

Thrombolysis Versus Percutaneous Coronary Interventions

- In general, PCI is the treatment of choice, provided it can be performed promptly by a qualified interventional cardiologist in an appropriate facility.
- In general, the maximum acceptable delay from presentation to balloon inflation is:
  - 90 minutes if a patient presents to a PCI-enabled hospital (door-to-balloon time).
  - 120 minutes if a patient is referred from another hospital (first medical contact to balloon time) with door-in door-out time in the first hospital <30 minutes.
- Fibrinolysis should be considered early when anticipated first medical contact (FMC)-to-device time at a PCI-capable hospital exceeds 120 minutes because of unavoidable delays. It should be performed within 30 minutes of arrival (door-to-needle time).
- Re-perfusion is not routinely recommended in patients who present more than 12 hours after symptom of onset.
- Beyond 12 hours, PCI may be of benefit in patients who continue to be symptomatic or develop cardiogenic shock or heart failure.

Re-perfusion Options for STEMI

Fibrinolysis is generally preferred
- Early presentation (≤3 hours from symptom onset) although PCI also equally effective
- Primary PCI is not an option for the following reasons
  - Catheterisation laboratory occupied/unavailable
  - Vascular access difficulties
  - Lack of access to a skilled PCI laboratory
- Delay to primary PCI
  - Door-to-balloon time minus door-to-needle time is >60 minutes
  - Door-to-balloon time is >90 minutes

Primary PCI is generally preferred
- Skilled PCI laboratory available with surgical backup
  - Door-to-balloon time is ≤90 minutes
  - Door-to-balloon time minus door-to-needle time is ≤60 minutes
- High risk from STEMI
  - Cardiogenic shock
  - Killip class CHF ≥3
- Contraindications to fibrinolysis including increased risk of bleeding and ICH
- Late presentation (>3 hours after symptom of onset)

Rescue PCI

- Rescue PCI is defined as PCI after failed fibrinolysis for patients with continuing or recurrent myocardial ischaemia.
- Indicated for patients with STEMI (aged < 75 years) who have received fibrinolytic therapy and have cardiogenic shock, severe CHF (Killip class III) or haemodynamically compromising ventricular arrhythmias.
- May also be performed in patients with persistent ischaemic symptoms.

Facilitated PCI

- Facilitated PCI refers to a strategy of planned immediate PCI after administration of an initial pharmacological regimen aimed at improving patency of coronary arteries before PCI. Such regimens may include GP IIb/IIIa inhibitors, full-dose or reduced-dose of fibrinolytic therapy, and combination of a GP IIb/IIIa inhibitor and a reduced-dose fibrinolytic agent.
- However, facilitated PCI is usually not recommended in most patients with STEMI.

Glycoprotein IIb/IIIa Inhibitors

- It is reasonable to use intravenous GP IIb/IIIa receptor antagonist such as abciximab, tirofiban or eptifibatide at the time of primary PCI in selected patients with STEMI who are receiving unfractionated heparin. These are contraindicated in patients receiving fibrinolytics.

Coronary Artery Bypass Grafting

- It is probably of little use in the setting of uncomplicated acute myocardial infarction. It offers benefit in patients with acute myocardial infarction with persistent pain or deteriorating haemodynamic status, and patients who develop coronary occlusion during coronary angiography and PTCA.

Management of Right Ventricular Infarction

- In this type of infarction there is reduced right ventricular stroke volume producing impaired left ventricular filling. This results in hypotension, raised JVP and clear lungs on auscultation.
- Volume expansion is the initial treatment of choice for haemodynamically significant right ventricular infarction.
- Avoid diuretics, ACE inhibitors and nitrates.
- Inotropics and vasodilators may also be required especially when a significant component of associated left ventricular dysfunction is also present.
- These patients should be routinely considered for re-perfusion therapy (fibrinolysis or PCI).

Management of Complications

Arrhythmias

- Pain relief, reassurance, rest and correction of hypokalaemia play a major role in prevention of arrhythmias.
- Manage congestive heart failure.
- Amiodarone is given after resuscitation from ventricular fibrillation, and for treatment of ventricular tachycardia with a rapid rate, multiple ectopic beats and R on T ectopics. Lidocaine, mexiletine or an intravenous β-blocker (atenolol or sotalol) may be used alternatively.
- DC cardioversion is the treatment of ventricular fibrillation.
- Verapamil, diltiazem, esmolol or digoxin is used to treat atrial tachycardia, flutter or fibrillation with a fast ventricular rate.
- Atropine is used to treat symptomatic sinus bradycardia and heart block.
- Temporary pacemaker in heart block complicating inferior wall infarction and anterior wall infarction.
- Cardiopulmonary resuscitation to treat asystole.

Cardiogenic Shock

- Management is discussed elsewhere.
- Cardiogenic shock is not a contraindication to fibrinolysis, but PCI is preferred if the patient is at a facility with PCI capabilities. PCI is reasonable in those who develop shock within 36 hours of symptom of onset and who are suitable candidates for re-vascularisation that can be performed within 18 hours of the onset of shock.
- Intra-aortic balloon counterpulsation (IABP) works synergistically with fibrinolytic agents or PCI in this setting.

Aftercare and Rehabilitation

- Restrict physical activities for 4–6 weeks since infarct takes 4–6 weeks to become replaced with fibrous tissue.
- Gradual mobilisation and return to work over 6 weeks.
- When there are complications the regimen has to be modified accordingly.
- Exercise within the limits set by angina and tiredness will do no harm but much good. Same limits apply to sexual activity.
- Control of obesity, regular exercises, cessation of smoking, adoption of a less frenetic way of life and control of plasma lipids by diets and drugs.

Medications

- Aspirin, 75–150 mg daily unless contraindicated.
- Clopidogrel, 75 mg daily for up to 12 months, in particular after stent implantation. May also be prescribed as an alternative when aspirin is contraindicated, or in addition to aspirin, particularly in patients with unstable angina or recurrent cardiac events.
- β-blocker unless contraindicated are continued indefinitely. Carvedilol, bisoprolol or metoprolol (extended release) should be used in patients with heart failure.
- ACE inhibitor given early after an acute coronary syndrome.
- Statin therapy initiated in hospital for all patients with coronary heart disease.
- Warfarin after myocardial infarction for those at high risk of systemic thromboembolism because of atrial fibrillation, mural thrombus, congestive heart failure or previous embolisation.
- Nitrates, short-acting for chest pain. Long-acting nitrates for symptom relief if β-blocker treatment alone is unsuccessful or is contraindicated.

- Aldosterone antagonist (e.g. spironolactone and eplerenone) considered early after myocardial infarction in those who have LVEF ≤40%, despite optimum doses of ACE inhibitors and β-blockers, and have either CHF or diabetes.

Q. Briefly discuss unstable angina and non-ST elevation myocardial infarction.

- Unstable angina and non-ST elevation myocardial infarction (NSTEMI) are part of acute coronary syndrome in which the patient presents with chest pain or its anginal equivalent (e.g. dyspnoea, jaw or arm pain) due to reduced coronary blood flow. They are also known as "non-ST segment elevation acute coronary syndrome" (NSTEACS).
- These are caused by coronary artery spasm, progression of the underlying CAD or haemorrhage into a non-occluding plaque with subsequent thrombosis producing coronary obstruction over a period of few hours.

Non-ST Elevation MI (NSTEMI)

- It is often characterised by ST depression and T inversion along with elevation in cardiac enzymes. In some cases however, ECG may be normal and only abnormality is elevated cardiac enzymes.
- The myocardial function as shown by ejection fraction is less deranged as compared to STEMI. However, early as well as late reinfarction rates are higher in the NSTEMI as compared to latter.

Unstable Angina (Ua)

- UA angina includes:
  - Exertional angina of recent onset (within 6 weeks) with ≥class III severity
  - Angina at rest or minimal exertion, generally lasting for >20 minutes
  - Angina of worsening severity as shown by increasing duration or severity of pain, pain occurring on exerting less as compared to previous episodes and increasing requirement of nitrates.
- The ECG is usually normal but may show ischaemic ST-T changes. Cardiac enzymes are normal.
- UA and NSTEMI differ primarily in whether the ischaemia is severe enough to cause sufficient myocardial damage to release detectable quantities of cardiac enzymes.
- Patients with UA are at a high risk of developing MI or sudden death as compared to patients with stable angina and therefore require aggressive treatment in the hospital.

Risk Categories in NSTEMI/UA

- Defines short-term risk of adverse effects in patients presenting with features suggestive of acute coronary syndrome and ECG showing no evidence of STEMI.
- As per one classification patient is classified into high-, intermediate- and low-risk categories.

	High risk *(Any of the following features)*	Intermediate risk *(No high-risk features, but presence of at least one of the following)*	Low risk *(No high-risk or intermediate-risk features; may have any of the following)*
History	• Accelerating tempo of ischaemic symptoms in preceding 48 hours	• Previous MI, peripheral or cerebrovascular disease, or CABG; previous aspirin use • Known diabetes with atypical symptoms of ACS	–
Character of pain	• Prolonged ongoing (>20 minutes) pain at rest	• Prolonged (>20 minutes) rest angina, now resolved, with moderate or high likelihood of CAD • Rest angina (>20 minutes) or relieved with rest or sublingual nitroglycerine • Nocturnal angina • New-onset or progressive class III or IV angina in the past 2 weeks without prolonged (>20 minutes) rest pain but with intermediate or high likelihood of CAD	• Increased angina frequency, severity or duration • Angina provoked at a lower threshold • New-onset angina with onset 2 weeks to 2 months before presentation

Clinical findings	• Pulmonary oedema, most likely because of ischaemia • New or worsening MR murmur • S₃ • New/worsening rales • Hypotension, bradycardia or tachycardia • Age ≥75 years	• Age ≥70 years	—
ECG	• Angina at rest with transient ST-segment changes >0.5 mm • Bundle branch block, new or presumed new • Sustained ventricular tachycardia	• New T wave inversion ≥2 mm • Pathologic Q waves or resting ST depression on ECG <1 mm in multiple lead groups (anterior, inferior, lateral)	• Normal or unchanged findings
Cardiac biomarkers	• Elevated troponin I or T, or CK-MB (e.g. cTnT or cTnI >0.1 ng/mL)	• Slightly elevated cardiac TnT, TnI, or CK-MB (e.g. cTnT or cTnI >0.01 ng/mL but <0.1 ng/mL)	• Normal

- Another classification is the use of TIMI (thrombolytics in myocardial infarction) risk score that uses a 7-point score. A score ≥3 predicts a high risk for death, non-fatal MI or severe ischaemia requiring urgent re-vascularisation at 14 days after presentation and therefore warrants early requirement of invasive management.

TIMI Score (One Point Score for Every Parameter)

• Age greater than or equal to 65 years • More than three coronary risk factors (early family history, as defined by infarction or sudden cardiac death in first degree male relatives age <55 years or in first degree female relatives age <65 years, diabetes mellitus, hypertension, hyperlipidaemia, or current smoking status) • Prior angiographic coronary obstruction (≥50%) • ST-segment deviation (≥0.5 mm)	• More than two angina events within 24 hours • Use of aspirin within 7 days • Elevated levels of cardiac biomarkers

Management

- Management of both NSTEMI and UA is similar. Patient should be hospitalised. Goals are to provide relief of ischaemia and to prevent recurrence of adverse ischaemic events.
- Risk stratify all patients with NSTEMI and UA to direct management decisions.
- Administer aspirin, oxygen (if saturation <90%), nitroglycerine, morphine and β-blockers as in patients with STEMI.
- Nitroglycerine (NTG): Patients with ongoing ischaemic discomfort should be given sublingual NTG every 5 minute for a total of 3 doses, If pain persists or patient develops heart failure or remains hypertensive, administration of intravenous NTG should be initiated (initial rate of 5–10 μg/minute with increases of 10 μg/minute every 3–5 minutes until symptoms are relieved or if systolic blood pressure falls below 100 mmHg). Nitrates should not be administered to patients with systolic blood pressure less than 90 mmHg or ≥30 mmHg below baseline, severe bradycardia (<50 beats/minute), tachycardia (>100 beats/minute) without heart failure, or right ventricular infarction.

- Calcium channel blockers: Routine use is not recommended. Diltiazem or verapamil may be administered as initial therapy for patients with ongoing ischaemia when β-blockers are contraindicated and there is no heart failure or left ventricular dysfunction.
- ACE inhibitors: ACE inhibitor for patients with hypertension despite treatment with NTG and a β-blocker, and with LV systolic dysfunction or CHF. Also recommended in presence of diabetes.
- An early invasive strategy (i.e., diagnostic angiography with intent to perform revascularisation) is indicated in patients who have refractory angina or haemodynamic or electrical instability, or who have high risk (see boxes above)
- Thrombolytic agents are contraindicated.

High-Risk Group

- Intravenous NTG if chest pain continues.
- Add loading dose of clopidogrel (600 mg) or prasugrel (60 mg) or ticagrelor (180 mg) followed by daily maintenance dose. These agents should be avoided if patient is likely to require emergency coronary bypass surgery (those with severe widespread ST-segment depression or haemodynamic instability).
- Anticoagulation: Add intravenous unfractionated heparin (60 U/kg as bolus and then 12 U/kg/hour infusion with monitoring of activated partial thromboplastin time (aPTT); goal is to maintain aPTT between 1.5 and 2.0 times the control) or subcutaneous low molecular weight heparin (e.g. enoxaparin) to antiplatelet agents in high-risk patients. Enoxaparin is slightly better than unfractionated heparin in terms of reducing mortality and recurrence of infarction, particularly if conservative treatment is planned. Other options include bivalirudin (in patients selected for an early invasive strategy) and fondaparinux (particularly for patients who are selected for a conservative treatment strategy and who are at an increased risk of bleeding). These drugs should continue for at least 48 hours after presentation.
- Platelet GP IIb/IIIa receptor antagonist is recommended in high-risk patients in whom an invasive strategy is planned. Administration should start as soon as a high-risk feature is identified. These drugs include eptifibatide, tirofiban and abciximab. Concomitant tirofiban is particularly beneficial and recommended in patients with diabetes. Abciximab should not be administered if PCI is not being planned. Risk of bleeding increases with concomitant use of aspirin and heparin.
- Statins: Lipid-lowering therapy with statins to be initiated upon hospital presentation for all patients regardless of baseline LDL cholesterol levels. The dose should be titrated later to maintain an LDL cholesterol concentration of 70 mg/dL or lower.
- Consider early coronary angiography (within 4–24 hours) and re-vascularisation even if patient becomes pain free.
- Consider immediate angiography and revascularisation in patients who do not become pain free after administration of medical therapy. Make these decisions with a target time of 30-45 minutes after arrival. Early intervention reduces risk of rehospitalisation and recurrent angina. It also reduces mortality and myocardial infarction over 5 years.

Intermediate-Risk Group

- Patients should undergo an accelerated diagnostic evaluation and further assessment to allow reclassification as low or high risk.

Low-Risk Group

- After an appropriate period of observation and assessment these patients may be discharged on medical therapy for outpatient follow-up. The medications include aspirin, a β-blocker, an ACE inhibitor and a statin.
- Another option for intermediate-risk and low-risk patients is to perform an early non-invasive testing (e.g. stress echocardiography, etc.). The goals of non-invasive testing are to determine whether ischaemia is present in patients with a low or intermediate likelihood of CAD and to estimate prognosis. It can be performed in patients who have been free of ischaemia at rest (or with low-level activity) and free of heart failure for a minimum of 12 to 24 hours. It can be performed during hospital stay or early after discharge in stable patients.

Q. Classify hypertension. Discuss the clinical features, complications and management of essential hypertension.

Q. Discuss the causes and investigations of secondary hypertension.

Q. Explain briefly about malignant hypertension.

- 15% of the general population can be regarded as hypertensive.

- Hypertension is defined arbitrarily at levels above generally accepted normals (Joint National Committee 8–JNC 8 recommendations).

Age ≥60 years	Systolic blood pressure >150 mmHg OR Diastolic blood pressure >90 mm Hg
Age <60 years	Systolic blood pressure ≥140 mmHg OR Diastolic blood pressure ≥90 mmHg
Age ≥18 years with diabetes or chronic kidney disease	Systolic blood pressure ≥140 mmHg OR Diastolic blood pressure ≥90 mmHg

- White coat hypertension
  - A transient increase in blood pressure in normal individuals when blood pressure is recorded in a hospital or in a physician's clinic.
  - Consider either carefully obtained home values using an appropriately calibrated BP monitor or obtaining 24-hour ambulatory BP measurements.
- Isolated ambulatory or masked hypertension
  - It is reverse phenomenon of "white coat hypertension" in which individuals with normal clinic blood pressure (<140/90 mmHg) may have elevated ambulatory or home blood pressure values.
  - Such individuals have been shown to have greater than normal prevalence of organ damage, with an increased prevalence of metabolic risk factors compared with subjects with a truly normal blood pressure.
- Paradoxical hypertension
  - Patients on antihypertensive agents, paradoxically show increase in blood pressure.
    - Patients with diabetes and hypertension on β-blockers develop paradoxical rise in blood pressure if they develop hypoglycaemia. This occurs due to sympathetic stimulation following hypoglycaemia.
    - Patients with bilateral renal artery stenosis who are given ACE inhibitors.
    - Administration of pure β-blockers to patients with phaeochromocytoma.

Classification

- Primary or essential hypertension
  - Accounts for 85% of the cases
  - Not possible to define a specific underlying cause
  - 70% of them have a positive family history
- Secondary hypertension
  - Accounts for 15% of the cases
  - Consequence of a specific disease or abnormality

Causes

Aetiology	
- Coarctation of aorta	
- Renal causes	Glomerulonephritis, chronic pyelonephritis, collagen vascular diseases, polycystic kidney disease, renal artery stenosis
- Endocrine causes	Phaeochromocytoma, Cushing's syndrome, Conn's syndrome, hyperparathyroidism, acromegaly, primary hypothyroidism, hyperthyroidism, congenital adrenal hyperplasia
- Alcohol and drugs	Oral contraceptives, anabolic steroids, corticosteroids, NSAIDs, COX-2 inhibitors, carbenoxolone, sympathomimetics, cyclosporin, sibutramine, bromocriptine, erythropoietin
- Pre-eclamptic toxaemia	
- Miscellaneous	Obstructive sleep apnoea

- Common causes of isolated systolic hypertension are:
  - Atherosclerosis
  - Aortic regurgitation
  - Patent ductus arteriosus
  - Thyrotoxicosis
  - Coarctation of aorta

Measurement of Blood Pressure

- BP must be measured twice—first with the patient supine or seated, then after the patient has been standing for ≥ 2 minutes on 3 separate days. The average of these measurements is used for diagnosis. Blood pressure in standing is required to exclude significant postural drop that may get accentuated with medications.
- Ideally patient should be sitting comfortably in a chair with back supported and both feet flat on the floor, no intake of caffeine or use of tobacco for at least 30–45 minutes before measurement, and resting with the arm supported at heart level for 5–10 minutes.
- BP is measured in both arms; if BP in one arm is much higher, the higher value is used. A difference of more than 10 mmHg between two arms suggests obstructive lesions of aorta, innominate artery or subclavian artery.
- An appropriately sized cuff covers two-third of the biceps; the bladder is long enough to encircle >80% of the arm, and bladder width equals at least 40% of the arm's circumference.
- The pressure at which the first heartbeat is heard as the pressure falls is systolic BP (phase I of Korotkoff sounds). Disappearance of the sound (phase V of Korotkoff sounds) marks diastolic BP.
- Auscultatory gap
  - Occasionally, after initial appearance of Korotkoff sounds at systolic pressure the sounds disappear for sometimes, and re-appear again and finally disappear at the diastolic pressure. This is auscultatory gap.
  - Seen in some patients with hypertension.
  - Overestimates diastolic pressure and underestimates systolic pressure depending upon which phase is auscultated. To avoid errors due to auscultatory gap, palpatory method of estimating systolic pressure should precede the auscultatory method.

Clinical Features

- There are three objectives of clinical examination:
  - Identify any underlying cause
  - Recognise risk factors for the development of complications
  - Detect any complications already present
- Risk factors are smoking, obesity, hyperlipidaemia, diabetes mellitus, and family history of premature CAD, all of which interact with hypertension, especially in the genesis of ischaemic heart disease.
- Clinical features of hypertension are due to hypertension *per se* and the underlying cause of hypertension.

Clinical Features due to Hypertension Per Se

- Majority are asymptomatic and hypertension is detected on routine examination.
- Acute hypertension causes transient headache and polyuria.
- Long-standing hypertension leads to left ventricular hypertrophy and heaving apical impulse.
- Left atrial hypertrophy and fourth heart sound.
- Aortic component (A_2) of second heart sound is accentuated.
- Very short early diastolic murmur.
- Fundal changes (refer complications).

Clinical Features due to Causes of Hypertension

- History of intake of alcohol or drugs like oral contraceptives, corticosteroids, NSAIDs, carbenoxolone or sympathomimetic agents.
- Radiofemoral delay, upper limb hypertension, collaterals around scapulae and systolic murmur over spine suggest coarctation of aorta.
- Panic attacks, paroxysmal headache and palpitations suggest phaeochromocytoma. Skin stigmata of neurofibromatosis may also suggest phaeochromocytoma.

- Recurrent back pain, undiagnosed fever and recurrent urinary infections suggest chronic pyelonephritis.
- Enlarged palpable kidneys in polycystic kidney disease.
- Bruit over the abdomen in the lumbar region suggests renal artery stenosis.
- Characteristic facies and habitus in Cushing's syndrome.

Complications of Hypertension

Central Nervous System Complications

- Transient ischaemic attacks
- Cerebrovascular accidents (strokes) due to cerebral thrombosis or haemorrhage
- Subarachnoid haemorrhage
- Hypertensive encephalopathy is characterised by very high blood pressure, neurological manifestations including transient disturbances in speech and vision, paraesthesia, seizures, disorientation, loss of consciousness and papilloedema. The neurological deficits are usually reversible with control of blood pressure.

Ophthalmic Complications

- Hypertensive retinopathy is characterised by thickening of the walls of the retinal arterioles, diffuse or segmental narrowing of blood columns, varying width of the light reflex from vessel walls, arterio-venous nipping, retinal haemorrhages, soft and hard exudates and papilloedema. Severe retinopathy can cause visual field defects and blindness.

Grading of Hypertensive Retinopathy

•	Grade I	Arteriolar narrowing and increase in light reflex over the arterioles
•	Grade II	Marked arteriolar narrowing and arteriovenous nipping
•	Grade III	Grade II plus flame-shaped haemorrhages and soft exudates
•	Grade IV	Grade III plus papilloedema

Cardiovascular Complications

- Coronary artery disease (angina and myocardial infarction)
- Left ventricular failure
- Aortic aneurysm
- Aortic dissection

Renal Complications

- Proteinuria
- Progressive renal failure

Malignant Hypertension

- It is a clinical syndrome of markedly high blood pressure with retinal haemorrhages and exudates, and often including confusion, headache, vomiting, visual disturbances and deterioration in renal functions.

When to Suspect a Secondary Cause in a Hypertensive Patient?

- Poor response to therapy (resistant hypertension)
- Worsening of control in previously stable patient
- Systolic pressure >180 mmHg or diastolic pressure >110 mmHg
- Onset of hypertension in persons below 20 years or older than age 50 years
- Significant hypertensive target organ damage
- Lack of family history of hypertension
- Findings on history, physical examination or routine investigations that suggest a secondary cause

Investigations

Basic Studies

- Urine analysis for protein, blood and glucose, and microscopic examination for casts or pus cells.
- Blood urea and creatinine (to assess renal function)
- Serum electrolytes (for hypokalaemia and alkalosis in hyperaldosteronism)
- Fasting and postprandial blood glucose (for hyperglycaemia)
- Serum cholesterol and triglycerides
- Serum calcium and uric acid
- Electrocardiogram (for left ventricular hypertrophy)
- Chest radiograph (for cardiac size, evidence of cardiac failure and aortic dilatation)

Secondary Studies

- Phaeochromocytoma—24 hours urinary catecholamine, metanephrines and VMA levels
- Cushing's syndrome—Plasma cortisol levels, 24 hours urinary cortisol and dexamethasone suppression test
- Renal artery stenosis—Captopril-entranced radionuclide scan (^{99m}technetium diethylenetriaminepenta acetic acid—DTPA scan), Doppler ultrasound, CT angiogram, MRI angiogram and renal arteriogram
- Polycystic renal disease—Ultrasonography, and intravenous urogram
- Primary aldosteronism—Hypokalaemia, high aldosterone levels and low plasma renin activity
- Acromegaly—GH levels and radiograph of the skull
- Primary hypothyroidism—T_3, T_4, and TSH levels
- Coarctation of aorta—Chest radiography for rib notching and catheterisation

Treatment

- Target for treating hypertension is as mentioned under JNC-8 recommendations.
- Treatment of hypertension can be discussed under three headings:
  - General measures
  - Antihypertensive drug therapy
  - Treatment of underlying cause (in secondary hypertension)

General Measures

- Lifestyle modifications are recommended for all patients with hypertension and pre-hypertension. A reduction in systolic blood pressure of 5 mmHg has been associated with about 10% reduction in mortality caused by stroke and heart disease,
  - Reassurance
  - Control of obesity
  - Low sodium diet (<100 mEq sodium or <6 g salt)
  - Other dietary recommendations—Diet rich in fruit, vegetables, potassium and low-fat dairy products, with low total and saturated fat (Dietary Approaches to Stop Hypertension or DASH eating plan)
  - Smoking to be abandoned
  - Alcohol consumption to be moderated (males no more than two alcoholic drinks of 30 mL per day and females no more than one per day)
  - Regular aerobic exercises
  - Relaxation classes, meditation and biofeedback

Antihypertensive Drug Therapy

Class	Drugs	Dose
• Diuretics		
• Thiazide diuretics	Chlorthalidone	12.5–25 mg OD
	Chlorothiazide	125–500 mg OD
	Hydrochlorothiazide	12.5–25 mg OD
	Metolazone	2.5–5.0 mg OD
	Indapamide*	1.25–2.5 mg OD

Class	Drugs	Dose
• Loop diuretics	Furosemide	10–40 mg BID (not used)
	Bumetanide	0.5–1.0 mg BID
	Torasemide or torsemide	2.5–10 mg OD
• Potassium-sparing diuretics	Amiloride	5–10 mg OD
	Triamterene	25–100 mg OD
• Aldosterone-receptor blockers	Spirolonolactone	25–100 mg OD
	Eplerenone	50–100 mg OD
• β-blockers	Propranolol	20–80 mg BID or TID
	Metoprolol	25–100 mg BID
	Atenolol	25–100 mg OD
	Bisoprolol	2.5–10 mg OD
	Nebivolol	5–10 mg OD
• Combined α- and β-blockers	Carvedilol	6.25–25 mg BID
	Labetalol	100–900 mg BID
• Angiotensin-converting enzyme (ACE) inhibitors	Captopril	12.5–50 mg TID
	Enalapril	2.5–20 mg OD or BID
	Lisinopril	2.5–40 mg OD
	Ramipril	2.5–20 mg OD
	Perindopril	2–8 mg OD
	Quinapril	10–80 mg OD
• Angiotensin II receptor antagonists	Losartan	25–50 mg BID
	Candesartan	8–32 mg OD
	Irbesartan	75–300 mg OD
	Valsartan	80–320 mg
	Telmisartan	20–80 mg OD
	Olmesartan	20–40 mg OD
• Direct rennin inhibitors	Aliskiren	75–300 mg OD
• Calcium channel blockers	Nifedipine (SR)	30–60 mg OD
	Verapamil	40–160 mg BID
	Diltiazem	40–160 mg BID
	Diltiazem (SR)	90–360 mg OD
	Amlodipine	2.5–20 mg OD
	Felodipine	2.5–20 mg OD
	Nicardipine (SR)	60–120 mg BID
• α-blockers	Prazosin	2.5–5.0 mg OD or BID
	Terazosin	1–20 mg OD
	Doxazosin	1–16 mg OD
• Direct vasodilators	Hydralazine	12.5–50 mg BID
	Minoxidil	1.25–40 mg BID
• Central α₂-blockers and other centrally acting drugs	Clonidine	0.05–0.3 mg BID
	α-methyldopa	250–1000 mg QID
	Reserpine	0.05–0.25 mg OD
	Moxonidine	0.2–0.3 mg OD or BID

*Indapamide has mild diuretic and vasodilator action

Diuretics

Thiazide Diuretics

- Mechanism of action—Thiazide diuretics have an influence on carbonic anhydrase and so they inhibit the reabsorption of sodium bicarbonate in proximal tubules. They depress the sodium and chloride reabsorption in the early distal convoluted tubules. Potassium depletion results from reduced $H+$ secretion and increased delivery of sodium and water to the distal tubules.
- Adverse effects—Impotence, postural hypotension, allergic rashes, marrow depression, hyperuricaemia, hypercalcaemia and diabetes.
- Useful as first-line agents in elderly patients with systolic hypertension. If blood pressure cannot be controlled with a thiazide diuretic, ACE inhibitors, angiotensin receptor blockers or calcium channel blockers may be added.

Loop Diuretics

- Furosemide or others are used if there is renal impairment or when greater sodium excretion is needed.

β Adrenoreceptor Antagonists (β-Blockers)

Uses of β-Blockers

• Angina pectoris	• Fallot's tetralogy (cyanotic spells)
• Acute myocardial infarction and post-myocardial infarction period (to prevent re-infarction)	• Phaeochromocytoma
• Chronic open-angle glaucoma	• Anxiety with somatic symptoms
• Cardiac arrhythmias	• Portal hypertension
• Hypertension	• Migraine prophylaxis
• Thyrotoxicosis	• Essential tremor
• Hypertrophic cardiomyopathy	

Contraindications of β-Blockers

• Chronic obstructive pulmonary disease and asthma	• Peripheral vascular disease
• Cardiac failure	• Diabetes mellitus (masks sympathetic signs of hypoglycaemia)
• Heart block	

Propranolol

- Mechanism of action includes sympatholytic effect, antihypertensive effect, and relief of anxiety, palpitation and angina.
- A large portion of the drug is destroyed in its first passage through liver.
- Treatment is started with 40 mg twice a day and gradually increased to 160 mg 6 hourly. Slow release forms are given as a single daily dose.
- Side effects—Gastric disturbances, bradycardia, cardiac failure, bronchospasm, tiredness, bad dreams, hallucinations, cold hands and muscle weakness.

Metoprolol and Atenolol

- Cardioselective β-1 antagonists with mechanism of action similar to that of propranolol. They have a greater effect on the cardiac β-1 receptors than on the β-2 receptors (β-2 receptors subserve bronchodilatation and vasodilatation).
- Dose—Metoprolol 50 mg twice daily to 100 mg thrice daily and atenolol 50–100 mg once daily. Sustained-release preparations of metoprolol are given in a dose of 12.5–100 mg OD.
- They may be used in hypertensive patients who have mild airway obstruction (COPD and asthma), peripheral vascular disease and type 1 diabetes; however caution is required.
- Other indications—Ischaemic heart disease and supraventricular tachycardia.
- Side effects—Same as for propranolol, but additionally cause hyperkalaemia.

Labetalol

- Mechanism of action is the same as that of propranolol. This has a combined α and β adrenoreceptor antagonistic action. Dose—100–200 mg twice daily. Side effects—Same as of propranolol.

Angiotensin Converting Enzyme (ACE) Inhibitors (Captopril, Enalapril, Lisinopril, Ramipril, and Perindopril)

- For a detailed account of ACE inhibitors, refer cardiac failure.
- Indicated as vasodilator therapy in hypertension and chronic cardiac failure.
- Mechanism of action includes powerful arteriolar and venous dilatation, and inhibition of aldosterone release.
- Contraindicated in patients with impaired renal function (creatinine >3 mg/dL) and bilateral renal artery stenosis.
- Dose—Start with a small dose (captopril 6.25 mg and enalapril 2.5 mg) and then gradually increase.
- Side effects—Cough, angio-oedema, postural hypotension, rashes, blood dyscrasias, neuropathy and diarrhoea.

Peripheral Vasodilators

- Act by producing peripheral arteriolar and venous vasodilatation by acting on arteriolar smooth muscles or smooth muscles of venules.
- Drugs in this category include hydralazine, prazosin, diazoxide, sodium nitroprusside and minoxidil.

Angiotensin Receptor Blockers

Mechanism of Action

- The renin–angiotensin–aldosterone system (RAAS) plays a pivotal role in the homeostatic regulation of blood pressure.
- Renin catalyses cleavage of angiotensinogen producing angiotensin I.
- Angiotensin II is produced from angiotensin I by the action of ACE. It is the most active hormone of the renin–angiotensin system.
- In humans, two angiotensin II receptors have been identified: AT_1 and AT_2. In adults, most effects of angiotensin II are mediated by the AT_1 receptor; the function of the AT_2 is not established.
- Binding of angiotensin II to its AT_1 receptors besides mediating its main biologic effects, including vasoconstriction, cell proliferation, hypertrophy and aldosterone secretion, provides feedback inhibition of further renin release by the kidney.
- Angiotensin receptor blockers block the action of angiotensin II by blocking AT_1 receptors.

Angiotensin Receptor Blockers

- Losartan
- Irbesartan
- Candesartan
- Valsartan
- Telmisartan
- Olmesartan

Side Effects

- Better tolerated compared to ACE inhibitors
- Side effects include hypotension, drowsiness and dizziness
- Cough is rare

Uses

- These agents are useful in the treatment of hypertension, myocardial infarction (to reduce myocardial remodelling) and diabetic nephropathy (to slow its progression).

Calcium Channel Blockers (Calcium Antagonists)

Uses of Calcium Channel Blockers

• Angina pectoris/Prinzmetal's angina	• Achalasia cardia
• Hypertension and hypertensive crisis	• Biliary dyskinesia
• Antiarrhythmic agent	• Pulmonary hypertension

- Peripheral vasospastic conditions, e.g. Raynaud's disease
- Migraine
- Subarachnoid haemorrhage (to prevent vasospasm)

- Cor pulmonale (chronic bronchitis with pulmonary hypertension)
- Congestive cardiac failure
- Valvular diseases—MR and AR

Nifedipine and Verapamil

- Mechanism of action—They act on cell membrane selectively to block the access of calcium and exert negative inotropic action. They increase myocardial oxygen supply, prevent coronary artery spasm, increase coronary blood flow and reduce peripheral vascular resistance.
- Dose—Nifedipine 10–20 mg three to four times daily and verapamil 180–360 mg/day in divided doses.
- Short-acting nifedipine, should be avoided.

Centrally Acting Drugs

Reserpine

- Mild antihypertensive with central and peripheral action. Dose—0.1–0.5 mg daily. Side effects—Nasal congestion, depression and parkinsonism.

α *Methyldopa*

- Mechanism of action—Both central and peripheral. Dose—250–500 mg twice or thrice daily. Side effects—Dryness of mouth, sedation, extrapyramidal features, fever, hepatitis and haemolytic anaemia.

Clonidine

- Mechanism of action—Central only. Dose—0.1–1.0 mg daily. Side effects—Dryness of mouth, drowsiness and rebound hypertension on sudden withdrawal.

Indications to Start Antihypertensive Drugs

- Antihypertensive drugs should be started if general measures do not help in bringing the blood pressure down:
  - In patients aged 60 years or more, initiate pharmacologic treatment to lower BP at systolic blood pressure (SBP) of 150 mmHg or higher or diastolic blood pressure (DBP) of 90 mmHg or higher and treat to a goal SBP lower than 150 mmHg and goal DBP lower than 90 mmHg.
  - In patients younger than 60 years, initiate pharmacologic treatment if SBP >140 mmHg or DBP > 90 mmHg. Goal is to reduce SBP <140 mm Hg and DBP <90 mm Hg.
  - In patients ≥18 years with chronic kidney disease or diabetes, initiate pharmacologic treatment if SBP >140 mm Hg or DBP >90 mmHg. Goal is to reduce SBP <140 mm Hg and DBP <90 mmHg.

Broad Guidelines on Selection of Drugs

- In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker.
- In the general black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or calcium channel blocker.
- In the population aged 18 years or older with chronic kidney disease and hypertension (irrespective of race and diabetic status), initial antihypertensive treatment should include an ACE inhibitor or aldosterone receptor blocking agent so as to improve kidney outcomes.
- If goal BP is not reached within a month of treatment, increase the dose of the initial drug or add a second drug from one of the other classes
- Additional points to remember are:
  - β-blockers are useful in young hypertensives and those with ischaemic heart disease.
  - Calcium channel blockers are useful in patients who have low renin levels, elderly patients who have a history of bronchial asthma and in those with peripheral vascular disease.
  - ACE inhibitors would be very beneficial in patients who have congestive cardiac failure.

Guidelines on Management of Hypertension


```
                    Hypertension in an adult
                              ↓
                    Lifestyle modifications
                              ↓
```

| • Age ≥60 years
• No DM
• No CKD | • Age <60 years
• No DM
• No CKD | • Age >18 years
• DM present
• No CKD | • Age >18 years
• CKD present
• DM ± |

| **BP goal:**
• Systolic <150
• Diastolic <90 | **BP goal:**
• Systolic <140
• Diastolic <90 | **BP goal:**
• Systolic <140
• Diastolic <90 | **BP goal:**
• Systolic <140
• Diastolic <90 |

| **Black:**
• Initiate thiazid-type diuretic or CCB | **Non-black:**
• Initiate thiazid-type diuretic or CCB or ACEI or ARB | **Black or non-black:**
• Initiate ACEI or ARB |

Blood pressure target not achieved

• Maximise first drug before adding second OR
• Add second medication from another class OR
• Start with 2 medication classes

DM – diabetes mellitus; CKD – chronic kidney disease; CCB – calcium channel blocker; ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin receptor blocker

Q. Discuss the clinical presentation and management of hypertensive encephalopathy.

- Hypertensive encephalopathy is characterised by a very high blood pressure and neurological disturbances including transient abnormalities in speech or vision, paraesthesia, disorientation, fits, loss of consciousness and papilloedema.
- Neurological deficit is fully reversible if the hypertension is properly controlled.

Treatment

- The initial aim of treatment is to rapidly lower the diastolic pressure to about 100 to 105 mmHg; this goal should be achieved within two to six hours, with the maximum initial fall in BP not exceeding 25% of the presenting value. Too rapid fall in blood pressure might cause cerebral ischaemia, blindness, myocardial infarction or renal insufficiency.
- Intravenous sodium nitroprusside (0.3–1.0 μg/kg/minute) is the most effective drug. It has to be used very carefully in an intensive care setup.
- Alternatively, parenteral labetalol (20 mg/minute to a maximum of 200 mg), hydralazine (5–10 mg every 30 minutes to a maximum of 300 mg) or nitroglycerine (5–100 μg/minute as infusion) may be used.
- Do not use sublingual nifedipine as it can produce precipitous fall in blood pressure leading to acute myocardial ischaemia or stroke.
- Bed rest, sedation and diuretics.

Q. Discuss briefly about hypertensive emergencies.

- A hypertensive emergency involves an elevated blood pressure (usually >180 mmHg systolic) in association with signs and/or symptoms of acute target organ damage. The resultant vascular compromise of affected organ may include hypertensive encephalopathy, acute heart failure with pulmonary oedema, dissecting aortic aneurysm, acute renal failure, unstable angina or myocardial infarction, intracranial bleed, acute ischaemic stroke or subarachnoid haemorrhage.
- In general, blood pressure should be lowered no more than 25% in the first 2 hours, with gradual lowering over the first 6 hours to a target of less than 160/100 mmHg.

Management of Hypertensive Emergencies

Diagnosis	Suggested drugs	Targets	Remarks
• Acute aortic dissection	• Labetalol IV • Esmolol bolus and then infusion • Nitroprusside infusion (after β-blockade)	• Systolic pressure <140 mmHg • Pulse <60/minute	• Avoid volume depletion • Use β-blockers before vasodilators
• Acute pulmonary oedema	• Nitroglycerine infusion • Enalaprilat IV • Nitroprusside infusion • Furosemide IV	• Reduce blood pressure by 20–30%	• Hypotension may occur with enalaprilat
• Acute coronary syndrome	• Nitroglycerine infusion • β-blockers (metoprolol or labetalol)	• Reduce blood pressure by no more than 20–30%	• Beware of hypotension in right ventricular infarction • Avoid hypotension
• Acute renal failure	• Labetalol IV • Nicardipine infusion • Dialysis	• Reduce blood pressure by no more than 20–30%	• Avoid nitroprusside • Avoid ACE inhibitors
• Hypertensive encephalopathy	• See above		
• Subarachnoid haemorrhage	• Labetalol bolus and infusion • Esmolol bolus and infusion • Nicardipine infusion	• Systolic pressure <160 mmHg or mean arterial pressure <130 mmHg (to reduce recurrence)	• Control of pain
• Intracranial bleed	• Labetalol bolus and infusion • Nitroglycerine infusion	• If fibrinolytic therapy planned, treat if >185/110 mmHg • Otherwise treat if >220/120 mmHg on third measurement done 15 minutes apart	• Avoid lowering blood pressure by more than 10–15% in 24 hours

Drugs used in Hypertensive Emergencies

Drug	Dose
• Labetalol	Bolus: 20 mg IV every 2 minutes or 40–80 mg every 10–20 minutes to a total of 300 mg OR Infusion: 2 mg/minute to a total of 300 mg
• Esmolol	250–500 µg/kg over 1–3 minutes, followed by 50 µg/minute; may be increased by 50 µg/minute every 4 minutes till response or till 200 µg/minute is reached. Every 4 minutes, additional loading doses can also be given

Drug	Dose
• Nicardipine	5 mg/hour; increase by 2.5 mg/hour every 15 minutes till response or 15 mg/hour is reached
• Nitroglycerine	Start at 5 μg/minute and increase by 5–10 μg/minute every 3–5 minutes till 200 μg/minute is reached
• Nitroprusside	0.3–0.5 μg/kg/minute; increase by 0.3–0.5 μg/kg/minute every 3–5 minutes to desired effect. Rates >2 μg/kg/minute may produce cyanide toxicity
• Enalaprilat	1.25 mg over 5 minutes IV every 4–6 hours

Q. Discuss the aetiology, pathophysiology, clinical features and investigations of pulmonary hypertension.

Q. Briefly explain about Graham Steell murmur.

Definition

- Pulmonary hypertension is an elevation in pulmonary vascular pressure that can be caused by an isolated increase in pulmonary arterial pressure or by increases in both pulmonary arterial and pulmonary venous pressures.
- In practice, pulmonary hypertension is the term used for pulmonary arterial hypertension and is defined as a resting mean pulmonary artery pressure greater than 25 mmHg

Aetiology and Classification (Dana Point Classification)

- Pulmonary arterial hypertension (PAH)
  - Idiopathic PAH
  - Heritable
  - Drug and toxin induced (fenfluramine, aminorex, toxic rape seed oil, amphetamines)
  - Associated with:
    - Connective tissue diseases (e.g. CREST syndrome, scleroderma, SLE, Sjogren's syndrome, polymyositis)
    - HIV infection
    - Portal hypertension
    - Congenital heart diseases
    - Schistosomiasis
  - Persistent pulmonary hypertension of the newborn
- Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)
- Pulmonary hypertension owing to left heart disease
  - Left ventricular systolic dysfunction
  - Left ventricular diastolic dysfunction
  - Valvular disease
  - Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
  - Pulmonary hypertension owing to lung diseases and/or hypoxia
  - Chronic obstructive pulmonary disease
  - Interstitial lung disease
  - Other pulmonary diseases with mixed restrictive and obstructive pattern
  - Sleep-disordered breathing
  - Alveolar hypoventilation disorders
  - Chronic exposure to high altitude
  - Developmental abnormalities
- Chronic thromboembolic pulmonary hypertension (CTEPH)

- Pulmonary hypertension with unclear multifactorial mechanisms
  - Haematologic disorders: Myeloproliferative disorders, chronic haemolytic anaemia, splenectomy
  - Systemic disorders: Sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
  - Metabolic disorders: Glycogen storage disease, Gaucher disease, thyroid disorders
  - Others: Tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

- In cirrhosis of liver, substances from the gastrointestinal tract are thought to escape hepatic metabolic pathways. They reach pulmonary circulation and cause vasoconstriction or obliterative vascular changes, leading to pulmonary hypertension.

Pathophysiology

- Normal pulmonary artery systolic pressure at rest is 18–25 mmHg, with a mean of 12–16 mmHg. This low pressure is due to the large cross-sectional area of the pulmonary circulation, which results in low resistance.
- Pulmonary hypertension results from one or both of the following:
  - Increase in pulmonary vascular resistance
  - Increase in pulmonary blood flow
- For a detailed account of the pathophysiology, refer the flow diagram given later.

Clinical Features

Symptoms of Pulmonary Hypertension and its Consequences

- Fatigue, dyspnoea, syncope and angina due to reduced cardiac output.
- Haemoptysis is uncommon and occurs due to rupture of distended pulmonary vessels.
- Peripheral oedema, tender hepatomegaly and raised jugular venous pressure due to right ventricular failure.
- Raynaud's phenomenon occurs in approximately 2% of patients with idiopathic pulmonary hypertension but is more common in patients with pulmonary hypertension related to connective tissue disease.

Signs of Pulmonary Hypertension

Cyanosis

- Peripheral cyanosis due to reduced cardiac output and skin blood flow.
- Central cyanosis occurs only when a patent foramen ovale permits right to left shunt.

Pulse

- Low volume pulse due to reduced cardiac output and left ventricular stroke volume.

Blood Pressure

- Narrow pulse pressure due to reduced cardiac output and left ventricular stroke volume.

Jugular Veins

- Prominent *a* waves.
- Jugular venous pressure is elevated with right ventricular failure.
- Prominent *v* waves and rapid *y* descent with functional tricuspid regurgitation.

Inspection and Palpation

- Apical impulse may be shifted indicating right ventricular hypertrophy and dilatation.
- Visible and palpable left parasternal heave and epigastric pulsations indicating right ventricular hypertrophy.
- Visible and palpable pulsations in the second left intercostal space from an underlying dilated pulmonary artery.
- Palpable pulmonary component (P_2) of second heart sound in the pulmonary area.

Auscultatory Signs in Pulmonary Hypertension

- Pulmonary ejection sound (ES)	- Pulmonary ejection systolic murmur (ESM)
- Abnormal second heart sound (S_2)	- Pulmonary early diastolic murmur (EDM)
- Right atrial fourth heart sound (S_4)	- Tricuspid pansystolic murmur (PSM)
- Right ventricular third heart sound (S_3)	

Pulmonary Ejection Sound (ES)

- It is a high-pitched, sharp, clicking sound heard in systole, best in the pulmonary area during expiration. A loud pulmonary ejection sound may radiate to the lower-left sternal border or even the apex.
- It results from dilatation of the pulmonary artery.

Abnormal Second Heart Sound (S₂)

- Loud pulmonary component (P_2) of second heart sound.
- Narrow splitting of the second heart sound (with right ventricular failure and the split widens).

Right Atrial Fourth Heart Sound (S₄)

- It is best heard at the lower left sternal border and becomes louder during inspiration.

Right Ventricular Third Heart Sound (S₃)

- It is a low-frequency sound, best heard at the lower left sternal border and becomes louder during inspiration.
- This is a sign of right ventricular failure.

Pulmonary Ejection Systolic Murmur (ESM)

- This is an ejection systolic murmur best heard at the pulmonary area.
- It results from the ejection of blood into a dilated pulmonary artery.

Pulmonary Early Diastolic Murmur (Graham Steell Murmur)

- This is a high-pitched, soft, blowing, decrescendo, early diastolic murmur which begins with or immediately after a loud P_2. It is usually confined to the second and third left intercostal spaces, and close to the sternum.
- The murmur results from pulmonary regurgitation secondary to pulmonary valve ring dilatation.

Tricuspid Pansystolic Murmur (PSM)

- This is a high-pitched PSM best heard at the lower left sternal border. The murmur increases in intensity during active inspiration ("inspiratory augmentation" or De-Carvallo's sign).
- The murmur results from functional tricuspid regurgitation secondary to the dilatation of tricuspid valve ring in right ventricular dilatation.
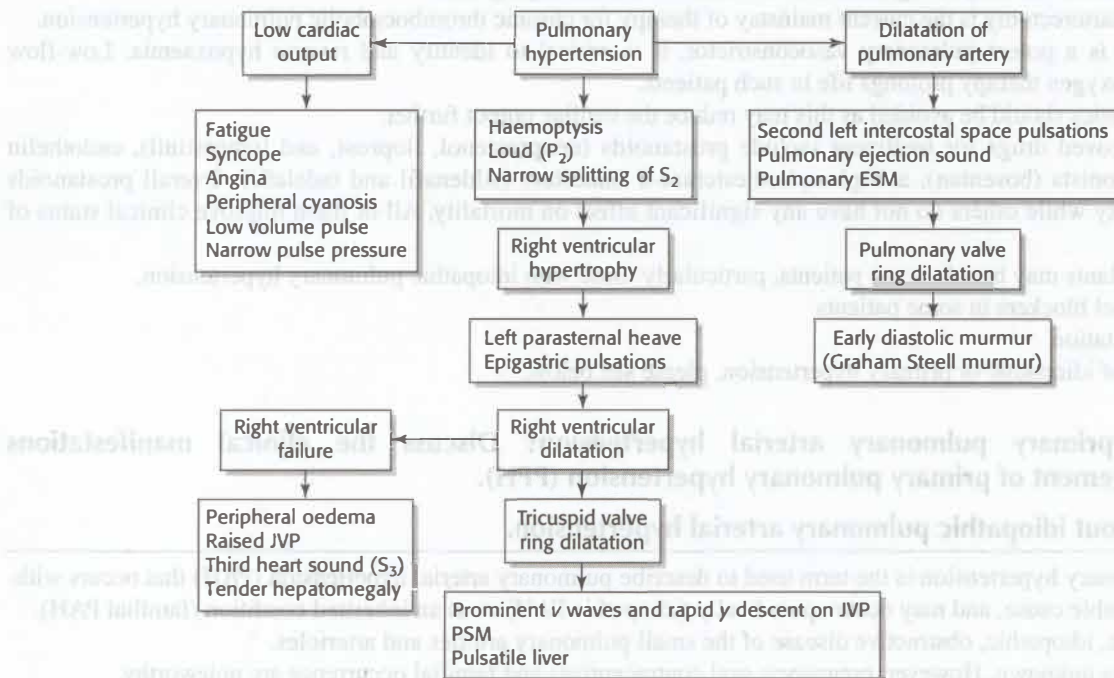
Pathophysiology of pulmonary hypertension

Investigations

- Electrocardiogram
  - Right axis deviation
  - Right atrial enlargement
  - Right ventricular hypertrophy
- Chest radiography
  - Enlargement of the pulmonary trunk and its main branches
  - Peripheral "pruning" of vascular shadows
  - Enlarged right atrium
  - Enlarged right ventricle
  - Findings of underlying lung or cardiac pathology
- Echocardiography is the most useful modality for detecting pulmonary HT and excluding underlying cardiac disease. It provides an estimate of pulmonary artery systolic pressure, left ventricular systolic and diastolic function, valvular disease and detects systemic-to-pulmonary shunt.
- Other tests
  - Comprehensive laboratory evaluation to clarify the aetiology. The goal is to identify or exclude treatable causes.
  - Initial tests include complete blood counts, prothrombin time, partial thromboplastin time and liver profile.
  - Autoantibodies if a collagen vascular disease is suspected.
  - HIV ELISA if the patient has risk factors.
  - Arterial blood gas to exclude hypoxia and acidosis as contributors to pulmonary hypertension.
  - Sleep studies if sleep apnoea suspected
  - Pulmonary function tests to establish airflow obstruction or restrictive lung disease
  - High-resolution computed tomography of chest to exclude occult interstitial lung disease
  - Helical CT to detect pulmonary thromboembolism
  - Ventilation–perfusion scanning to differentiate chronic thromboembolism from primary pulmonary hypertension
  - Right heart catheterisation in patients with unexplained pulmonary hypertension. It is also required to diagnose PAH, assess the severity of haemodynamic deterioration and analyse vasoreactivity of pulmonary circulation so as to identify patients who may benefit from treatment with calcium channel blockers.

Treatment

- Treatment is directed at early recognition and treatment of the underlying cause.
- Pulmonary endarterectomy is the current mainstay of therapy for chronic thromboembolic pulmonary hypertension.
- Since hypoxia is a potent pulmonary vasoconstrictor, it is critical to identify and reverse hypoxaemia. Low-flow supplemental oxygen therapy prolongs life in such patients.
- Excessive diuretics should be avoided as this may reduce the cardiac output further.
- Currently approved drugs for treatment include prostanoids (epoprostenol, iloprost, and treprostinil), endothelin receptor antagonists (bosentan), and phosphodiesterase-5 inhibitors (sildenafil and tadalafil). Overall prostanoids reduce mortality while others do not have any significant effect on mortality. All of them improve clinical status of patients.
- Oral anticoagulants may benefit some patients, particularly those with idiopathic pulmonary hypertension.
- Calcium channel blockers in some patients
- Lung transplantation
- For treatment of idiopathic or primary hypertension, please see below.

Q. What is primary pulmonary arterial hypertension? Discuss the clinical manifestations and management of primary pulmonary hypertension (PPH).

Q. Discuss about idiopathic pulmonary arterial hypertension.

- Primary pulmonary hypertension is the term used to describe pulmonary arterial hypertension (PAH) that occurs without a demonstrable cause, and may occur sporadically (idiopathic PAH) or as an inherited condition (familial PAH).
- It is an intrinsic, idiopathic, obstructive disease of the small pulmonary arteries and arterioles.
- The aetiology is unknown. However, pregnancy, oral contraceptives and familial occurrence are noteworthy.
- Primary pulmonary hypertension is more common in females (female to male ratio is 5:1). The mean patient age is 20–30 years. Death commonly occurs within 5 years of the onset of symptoms.

- Clinically dyspnoea, weakness, fatigue, exercise-induced syncope and chest pain in an otherwise healthy, young, acyanotic female with no history of heart disease or cardiac murmurs suggest primary pulmonary hypertension. Sudden death is common.
- Physical signs are the same as that for pulmonary hypertension.
- As many as 40% of patients with idiopathic PAH have serologic abnormalities, usually an antinuclear antibody in a low titre and non-specific pattern.
- Other investigations have been described above.

Management

- Restrict physical activities. Encourage cautious, graduated physical activity. Heavy physical activity can precipitate exertional syncope.
- Hot baths are discouraged because the resultant peripheral vasodilatation can produce systemic hypotension and syncope.
- Avoid excessive sodium intake.
- Careful use of diuretics in patients with right ventricular failure and functional tricuspid regurgitation.
- Supplemental oxygen if oxygen saturation falls below 90%.
- Calcium channel blockers (nifedipine or verapamil) may alleviate pulmonary vasoconstriction and prolong life in about 20% cases. They should only be given to those who show response on cardiac catheterisation. However, verapamil should be avoided because of its negative inotropic effect.
- Epoprostenol (a prostacyclin) is a potent short-acting vasodilator. Continuous intravenous infusion of this agent has been shown to prolong life. Iloprost, another prostacyclin has also been used intravenously or via nasal route.
- Endothelin-I receptor antagonists, (e.g. bosentan) and selective phosphodiesterase-5 inhibitors (e.g. sildenafil) are useful in some patients.
- Chronic anticoagulation with warfarin is recommended to prevent thrombosis in patients with primary pulmonary hypertension. Maintaining an International Normalised Ratio (INR) of 1.5–2.5 is recommended.
- Atrial septostomy—creation of a right-to-left interatrial shunt to decompress the failing pressure- and volume-overloaded right heart. May be used as a palliative procedure or as a stabilising bridge to lung transplantation.
- Ultimate answer is lung transplantation (with or without heart transplantation).

Q. Discuss the risk factors, clinical features, investigations and treatment of venous thrombosis (deep venous thrombosis—DVT).

Q. Discuss the prophylaxis of venous thrombosis (deep venous thrombosis—DVT).

Q. Explain about Wells probability score.

- Venous thrombosis implies thrombus formation in the systemic or right side of the heart.
- Deep venous thrombosis (DVT) means thrombus formation in the deep venous system, especially of the lower extremities and pelvis.

Significance

- Venous thrombi can embolise to lung resulting in pulmonary embolism (pulmonary thromboembolism—PTE) and cause pulmonary infarction.
- It is during the first few days (7–10 days) after the formation of the thrombus that embolic risk is highest.

Common Sites of Venous Thrombosis

- Deep venous system of lower extremities (95% of pulmonary emboli arise from here)
- Other systemic veins, especially pelvic veins
- Right atrium, especially in patients with atrial fibrillation and cardiac failure
- Right ventricle

Pathogenesis

- The three factors which promote DVT are defined by Virchow:
  - Stasis of blood
  - Abnormalities of vessel wall
  - Hypercoagulable state

Risk Factors of Venous Thrombosis (also see Section on Prophylaxis)

Biochemical

- Disorders with hypercoagulable states (e.g. antithrombin deficiency, protein C deficiency, protein S deficiency, antiphospholipid syndrome, etc.)

Clinical

- Low cardiac output
- Obesity, advancing age
- Prolonged bed rest, post-partum period
- Dehydration, polycythaemia

- Long surgical procedures under GA
- Fractures or injuries of lower limbs
- Left and right ventricular failure
- Carcinoma, use of oestrogens

Clinical Features of Deep Venous Thrombosis (DVT)

- Clinical detection is difficult as DVT is silent in 50% of cases.
- Low-grade fever.
- Pain, tenderness, warmth and swelling of calf muscles.
- "Homan's sign" is pain in the calf on forceful dorsiflexion of foot.
- Later, there is cyanosis, oedema and venous gangrene of the affected limb.

Wells Clinical Prediction Guide for Diagnosis of DVT

- Quantifies pretest probability of DVT.
- Stratifies patients into high-, moderate-, or low-risk categories for having DVT.

Wells Probability Score

Clinical parameter	Score
• Active cancer (treatment ongoing or within 6 months or palliative)	+1
• Paralysis or recent plaster immobilisation of the lower extremities	+1
• Recently bedridden for >3 days or major surgery <4 weeks	+1
• Localised tenderness along the distribution of the deep venous system	+1
• Entire leg swollen	+1
• Calf swelling >3 cm compared to the asymptomatic leg	+1
• Pitting oedema (greater in the symptomatic leg)	+1
• Previous DVT documented	+1
• Collateral superficial veins (non-varicose)	+1
• Alternative diagnosis (at least as likely as DVT)	−2
Low probability = score ≤0; moderate probability = score 1 or 2; high probability = score ≥3	

Complications

- Venous gangrene
- Pulmonary embolism
- Post-thrombotic syndrome (oedema, nocturnal cramping, venous claudication, skin pigmentation, dermatitis, ulceration and life-long limb pain)

Investigations

- D-dimer is elevated (500 ng/mL) in most patients but is not specific. Also elevated in trauma, recent surgery, haemorrhage, cancer, elderly, pregnancy and sepsis. In DVT, it remains elevated for 7 days. D-dimer results should be used as follows:
  - A negative D-dimer assay rules out DVT in patients with low-to-moderate risk and a Wells score ≤1.
  - All patients with a positive D-dimer assay and all patients with a moderate-to-high risk of DVT (Wells score ≥2) require a diagnostic study (Doppler ultrasonography).

- Doppler (duplex) ultrasonography is useful, but highly operator dependent. The major criterion for detecting venous thrombosis is failure to compress the vascular lumen. Absence of normal phasic Doppler signals arising from the changes in venous flow provide indirect evidence of venous occlusion.
- Ascending contrast venography (phlebography) is the best method but is rarely performed presently due to availability of Doppler ultrasound.
- Impedance plethysmography (IPG) accurately detects above-knee thrombi. However, it cannot distinguish between thrombotic occlusion and extravascular compression of the vein.
- Radiofibrinogen method is very accurate in calf vein and lower thigh thrombi. However, results can be obtained only after several hours of injecting radiofibrinogen.

Algorithm for Diagnosing DVT
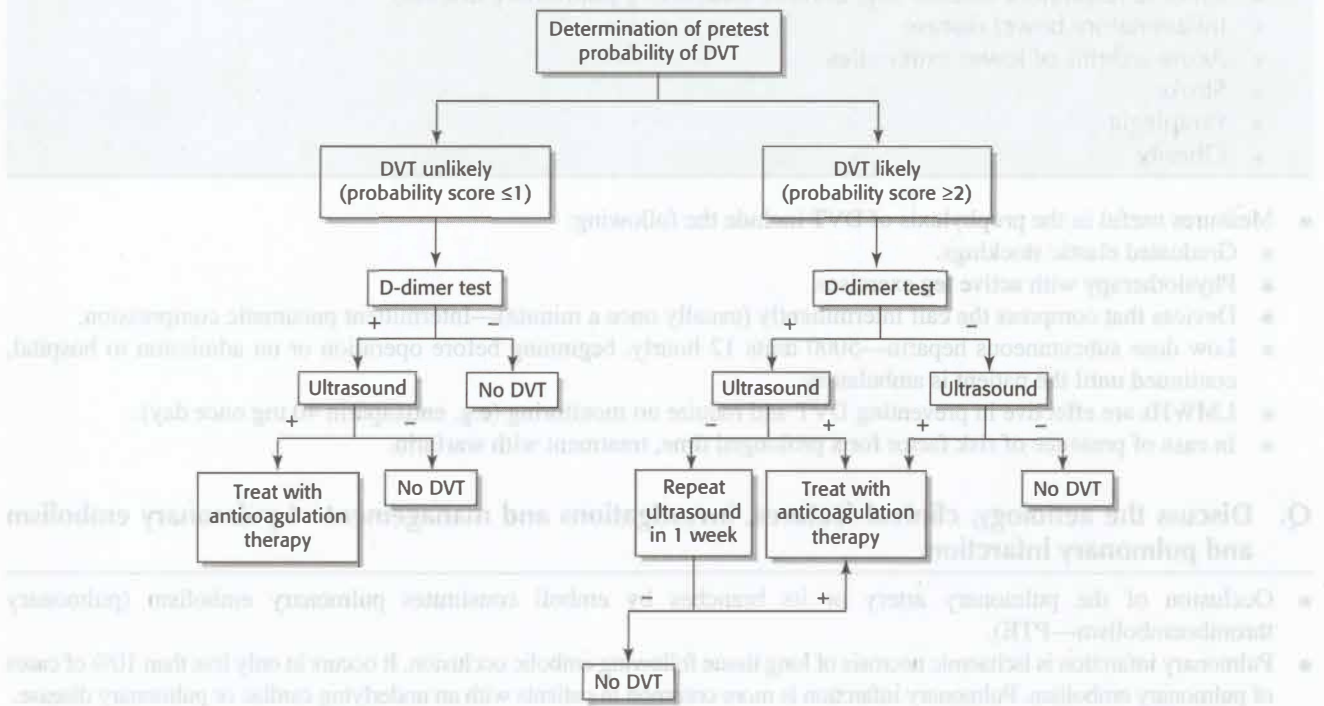
Treatment of Deep Venous Thrombosis (DVT)
- Bed rest with legs elevated to 15°.
- Physiotherapy to legs.
- Graduated elastic stockings (compression stockings) should be used routinely to prevent post-thrombotic syndrome, beginning within 1 month of diagnosis of proximal DVT and continuing for a minimum of 1 year after diagnosis.
- Start treatment with heparin (as in pulmonary embolism) as well as warfarin and continue with warfarin. No loading dose of warfarin is recommended at present. Anticoagulation with warfarin should be maintained for 3–6 months for DVT secondary to transient risk factors, and for more than 12 months for recurrent DVT (with INR between 2.0 and 3.0). For idiopathic DVT anticoagulation should be continued for at least 6 months, though extended-duration therapy may be more beneficial.
- Low molecular weight heparins (LMWHs) may be used in place of conventional heparin in the initial period. Consistent evidence demonstrates that LMWH is superior to unfractionated heparin for the initial treatment of DVT. Outpatient treatment of DVT with LMWH is safe and cost-effective for carefully selected patients.
- Thrombolysis with streptokinase has little role in DVT as its efficacy in preventing embolism may not be better than heparin. One area where thrombolytic therapy is increasingly useful is when using catheter-guided lytic therapy to re-canalise the vein in massive DVT, involving common femoral or iliac system.
- Thrombectomy (rarely).
- Inferior vena cava filters in patients with acute proximal DVT of the leg and contraindication to anticoagulation.
- Early ambulation is recommended over initial bed rest unless patient has severe pain or oedema.
- Compression stockings are advisable as they reduce incidence of post-thrombotic syndrome

Prophylaxis

- Prophylaxis is indicated in patients at high risk for DVT and pulmonary embolism.

- Fractures of pelvis or extremities
- Those undergoing major abdominal, thoracic or gynaecological surgery
- Major medical diseases in admitted patients:
  - Acute coronary syndrome
  - Acute congestive failure (NYHA classes III, IV)
  - Active cancer requiring therapy
  - Sepsis
  - Acute respiratory diseases (respiratory failure with or without mechanical ventilation)
  - Chronic respiratory disease (e.g. chronic obstructive pulmonary disease)
  - Inflammatory bowel disease
  - Acute arthritis of lower extremities
  - Stroke
  - Paraplegia
  - Obesity

- Measures useful in the prophylaxis of DVT include the following:
  - Graduated elastic stockings.
  - Physiotherapy with active leg exercises.
  - Devices that compress the calf intermittently (usually once a minute)—Intermittent pneumatic compression.
  - Low dose subcutaneous heparin—5000 units 12 hourly, beginning before operation or on admission to hospital, continued until the patient is ambulatory.
  - LMWHs are effective in preventing DVT and require no monitoring (e.g. enoxaparin 40 mg once day).
  - In case of presence of risk factor for a prolonged time, treatment with warfarin.

Q. Discuss the aetiology, clinical features, investigations and management of pulmonary embolism and pulmonary infarction.

- Occlusion of the pulmonary artery or its branches by emboli constitutes pulmonary embolism (pulmonary thromboembolism—PTE).
- Pulmonary infarction is ischaemic necrosis of lung tissue following embolic occlusion. It occurs in only less than 10% of cases of pulmonary embolism. Pulmonary infarction is more common in patients with an underlying cardiac or pulmonary disease.

Types

- Acute massive pulmonary embolism where the embolus lodges in the main pulmonary artery (may result in death).
- Pulmonary infarction from embolism to smaller pulmonary artery.
- Recurrent silent pulmonary embolism resulting in chronic pulmonary hypertension and chronic right heart failure.

Consequences of Pulmonary Embolism

Immediate Consequences

- The immediate effect of pulmonary embolism is a complete or partial obstruction of the pulmonary arterial blood flow to the distal lung. This results in the following consequences:
  a. Respiratory consequences
     - "Wasted ventilation" resulting from embolic occlusion producing a zone of lung that is ventilated but not perfused
     - Loss of alveolar surfactant resulting in alveolar collapse and frank atelectasis
     - Arterial hypoxaemia
  b. Haemodynamic consequences
     - Acute pulmonary hypertension
     - Acute right ventricular failure
     - Pulmonary infarction
     - Shock in massive embolism
     - The severity of haemodynamic consequences depends on the extent of embolic obstruction. At least 50% of vascular area must be obstructed for significant elevation of pulmonary arterial pressure.

Late Consequences

- Vast majority of pulmonary emboli resolve, while few do not.
- Recurrent "silent" small pulmonary emboli present only with late consequences like pulmonary hypertension and chronic right heart failure.

Causes and Risk Factors

- Pulmonary embolism usually results from dislodgement of venous thrombi of the deep veins of lower limbs and pelvis. Rarely, emboli can arise from right atrium or right ventricle.
- Causes of pulmonary embolism are the same as that for venous thrombosis (refer venous thrombosis).
- Risk factors (predisposing factors) of pulmonary embolism are the same as that for venous thrombosis (refer venous thrombosis).
- "Economy class syndrome" (or traveller's thrombosis) is a rare condition. The incidence through various studies appears to be in the range of 0.25/1,00,000 passengers in flights longer than 8 hours. An increased risk of thrombosis has not yet been confirmed in flights of less than 4 hours.

Clinical Features of Pulmonary Embolism and Pulmonary Infarction

- Sudden onset of unexplained breathlessness
- Retrosternal discomfort from right ventricular ischaemia
- Syncope
- Haemoptysis
- Pleuritic chest pain and haemoptysis in pulmonary infarction
- Supraventricular tachyarrhythmias
- Sudden onset or worsening of congestive heart failure
- Sudden deterioration in a patient with chronic obstructive lung disease

Physical Findings

- There may be no abnormal physical findings.
- A low-grade fever may occur with infarction.
- Central cyanosis in massive pulmonary infarction.
- Pleural friction rub and a small pleural effusion may be seen with pulmonary infarction.
- Tachycardia is the most consistent and most important physical sign.
- In a massive pulmonary embolism following signs may be present:
  - Raised JVP with prominent *a* waves
  - Left parasternal (right ventricular) lift
  - Loud pulmonary component (P_2) of second heart sound
  - Wide splitting of second heart sound indicating severe pulmonary hypertension and right ventricular failure
  - Right ventricular third heart sound (RVS_3 or RV gallop)
  - Ejection systolic murmur at pulmonary area
  - Clinical evidence of DVT may be present (refer venous thrombosis)

Wells Scoring System

- To determine probability of pulmonary embolism, Wells scoring system is used.

Parameter	Score
• Symptoms of DVT	3
• PE most likely diagnosis	3
• Heart rate >100/minute	1.5
• Immobilised in past 4 weeks	1.5
• Previous PE or DVT	1.5
• Haemoptysis	1
• Malignancy	1
Clinical probability of PE: high if score >6; intermediate if score 2–6; low if score <2	

Diagnosis

- The possibility of pulmonary embolism should be considered if a patient has pleuritic chest pain, syncope, haemoptysis or dyspnoea out of proportion to the size of pleural effusion.

- Polymorphonuclear leucocytosis and raised erythrocyte sedimentation rate (ESR) with pulmonary infarction.
- Electrocardiogram may show tachycardia, changes of acute pulmonary hypertension and right ventricular enlargement with strain. Other abnormalities include atrial fibrillation or flutter; an S wave in lead I, a Q in Lead III and an inverted T in lead III (S_1, Q_3 and T_3 pattern).
- Arterial blood gas studies may reveal hypoxaemia, hypocapnia and respiratory alkalosis.
- The best screening test is a measurement of the D-dimer levels in the blood. If a sensitive D-dimer test is negative, the diagnosis of embolism is essentially ruled out (unless patient has a high risk of PTE clinically).
- If D-dimer test is positive, additional specific diagnostic tests include Doppler of legs for deep vein thrombosis, spiral CT pulmonary angiography (CT-PA), perfusion scanning of the lungs and pulmonary angiography.
  - A normal perfusion scan excludes a diagnosis of significant pulmonary embolism. However, an abnormal perfusion scan can be due to underlying lung pathology. A ventilation–perfusion scan is required in such cases even though it may still give ambiguous results.
    - A V/Q scan uses less radiation and contrast. The results of V/Q scanning are most often given as high, intermediate or low probability.

Radiological Features

Pulmonary embolism
- Normal
- Increased radiolucency in lung zones due to diminished or absent blood flow
- Small infiltrative shadows due to atelectasis
- Elevation of the hemidiaphragm
- Difference in the diameter of pulmonary arteries and their main branches on either side
- Abrupt "cut-off" of a vessel

Pulmonary infarction
- May be normal, especially in early stages
- Parenchymal, wedge-shaped, infiltrative shadow abutting against the pleura (usually appears 12–36 hours later)
- Small pleural effusion

Algorithm for Diagnosis of Pulmonary Embolism
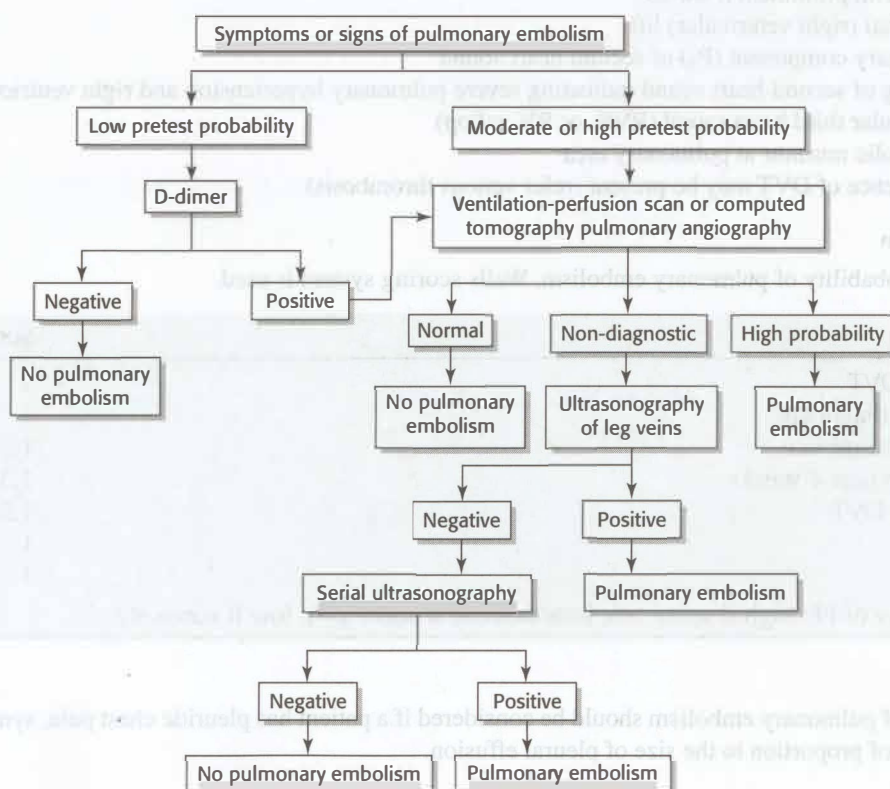
Management

Supportive Measures

- Bed rest in acute stage
- Oxygen and analgesics
- Intravenous saline and/or noradrenaline may be necessary to maintain venous pressure in massive embolism

Anticoagulation

- Unfractionated heparin is given at an initial dose of 80 units/kg intravenously, followed by maintenance.
- For maintenance, any one of the following three regimens may be used:
  - Continuous intravenous
  - Intermittent intravenous
  - Intermittent subcutaneous
- "Continuous intravenous maintenance" is the most popular. Here, heparin is administered using an infusion pump at a rate of 18 units/kg/hour.
- Heparin therapy is monitored with clotting time (CT) and activated partial thromboplastin time (aPTT) which is maintained at 1½–2 times the control value.
- Intravenous heparin therapy should be continued for 5-7 days.
- Heparin prevents additional thrombus formation and permits the endogenous fibrinolytic system to lyse the clot in the pulmonary arteries.
- Low molecular weight heparins (enoxaparin, dalteparin, tinzaparin) have been shown to be more efficacious as they reduce the mortality as compared to the conventional heparin. Monitoring of the patient by performing repeated aPTT is also not required. Enoxaparin may be used in a dose of 1 mg/kg twice a day subcutaneously.
- An alternative to low molecular weight heparin is fondaparinux.
- Along with heparin, oral warfarin should be started with the intention of keeping the INR at 2.5–3.0. This may take 4–5 days after which heparin is stopped.
- Anticoagulation is maintained for at least 6 months.

Thrombolytic Therapy

- It is used in patients with major embolism with hypotension (systolic blood pressure <90 mmHg).
- Agents currently used for thrombolysis are:
  - Streptokinase
  - Tenecteplase
  - Tissue plasminogen activator (tPA)

Surgical Therapy

- Inferior vena cava filters to prevent recurrent emboli.
- Venous interruption
- Pulmonary embolectomy (consider in patients with cardiac arrest or refractory hypotension).

Prophylaxis

- Prophylactic measures to prevent pulmonary embolism are the same as that for venous thrombosis.

Q. Discuss the aetiology, clinical features, investigations, complications and management of acute myocarditis.

- Myocarditis is defined as an inflammatory process of myocardium. It may be fulminant, acute or chronic.

Aetiology

• Infections	Viral (Coxsackie A and B, adenoviruses, influenza, HIV, dengue virus, parvovirus B19, hepatitis C, Epstein-Barr virus,), bacterial (diphtheria, *Staph. aureus, Mycoplasma pneumoniae*), protozoal (trypanosomiasis, toxoplasmosis), spirochaetal (Lyme disease), fungal

• Collagen vascular diseases	Scleroderma, systemic lupus erythematosus, polyarteritis nodosa
• Hypersensitivity reactions	Drugs: Azithromycin, benzodiazepines, clozapine, cephalosporins, dapsone, gefitinib, lithium, loop diuretics, methyldopa, NSAIDs, penicillins, phenobarbital, smallpox vaccination, streptomycin, sulphonamides, tetanus toxoid, tetracycline, thiazide diuretics, tricyclic antidepressants
	Others: Bee venom, wasp venom, scorpion venom, snake venom
• Miscellaneous	Acute rheumatic fever, drugs (anthracyclines), toxins (cocaine, alcohol, arsenic), chemical agents, radiation, sarcoidosis, Kawasaki disease, thyrotoxicosis, coeliac disease

Clinical Features of Acute Myocarditis

- Range from asymptomatic ECG changes to cardiogenic shock.
- May have a viral prodrome of fever, myalgias, respiratory symptoms or gastroenteritis followed by an abrupt onset of haemodynamic collapse.
- May present with acute chest pain. Chest pain in acute myocarditis may mimic typical angina and be associated with electrocardiographic changes, including ST segment elevation.
- Physical examination may be normal.
- Other findings include:
  - Inappropriate tachycardia
  - Muffled first heart sound
  - Third heart sound
  - Murmur of mitral regurgitation
  - Pericardial friction rub in associated pericarditis
  - Arrhythmias including conduction blocks
  - Features of congestive heart failure
- Major cause of sudden death in patients below the age of 40 years.

Investigations

- Laboratory tests may show leucocytosis, elevated ESR or eosinophilia.
- Creatine kinase-MB enzyme and troponin T may be elevated in small number of patients. CK-MB not generally useful for non-invasive screening because of its low predictive value.
- Electrocardiogram may show non-specific ST-T changes (elevation or depression), blocks or arrhythmias.
- Chest radiography may show cardiomegaly.
- Echocardiography is useful to assess cardiac functions and exclude any associated valvular abnormality. Classic findings include global hypokinesia with or without pericardial effusion.
- Routine viral serology testing is not recommended.
- Contrast-enhanced MRI and indium[111]-labelled antimyosin scintigraphy are non-invasive tests to identify myocardial inflammation. MRI can also differentiate myocarditis from myocardial infarction.
- Endomyocardial biopsy can confirm the diagnosis. PCR helps to diagnose specific viral pathogens in the myocardium. However, its utility is limited because of sampling error from patchy inflammatory infiltrates and variability in observer interpretation. Indications include:
  - Patients with new-onset heart failure (< 2 weeks) associated with a normal or dilated left ventricle with haemodynamic compromise.
  - Patients with new-onset heart failure of 2 weeks to 3 months' duration with a dilated left ventricle, ventricular arrhythmia or high-degree atrioventricular blockade.
  - Patients whose condition fails to respond to treatment in 1 to 2 weeks.

Complications

- Arrhythmias and heart block
- Congestive heart failure
- Acute pericarditis
- Progression to chronic myocarditis
- Progression to chronic dilated cardiomyopathy

Natural History

- Variable course.
- Myocarditis masquerading as myocardial infarction almost universally results in a full recovery of cardiovascular status in previously healthy adults.
- Patients with fulminant myocarditis (rapid onset of symptoms and severe haemodynamic compromise at presentation) have a good long-term survival rate if patients survive the initial phase.
- Patients with acute myocarditis in whom development of symptoms is more protracted and the clinical picture less dramatic often have a worse long-term outcome.
- Patients who present with mildly compromised ventricular function (left ventricular ejection fraction of 40–50%) typically improve within weeks to months.
- Among those presenting with more advanced left ventricular dysfunction (LVEF ≤35%) 50% will develop chronic ventricular dysfunction.

Management

- Prolonged bed rest in severe cases and restriction of physical activities in less severe cases (till ECG is normal).
- Treatment of congestive heart failure (using ACE inhibitors, β-blockers, and diuretics) and arrhythmias (using amiodarone and β-blockers).
- Aldosterone antagonists (eplerenone or spironolactone) in patients not responding to above treatment.
- In severe congestive failure, intravenous nitroglycerine or sodium nitroprusside may be required to reduce high filling pressures. If forward flow is a problem, inotropic agents (milrinone and dobutamine) may be used.
- Digoxin should be used with caution and at low doses only.
- Anticoagulation in the setting of concomitant atrial fibrillation or arterial or venous thromboembolism.
- Immunosuppressives (including steroids and azathioprine) should not be used in the routine treatment of patients with myocarditis. However, these agents are very useful in the treatment of patients with cardiac involvement due to a systemic autoimmune disease, sarcoidosis or hypersensitivity reaction. They are also useful in chronic dilated cardiomyopathy where symptoms last for more than 6 months. Interferons have been used in many patients with variable results.
- Ventricular assist devices and intra-aortic balloon pump in refractory patients that may provide a bridge to transplant or to recovery.
- Extracorporeal membrane oxygenation (ECMO) as a short-term bridge to transplant or recovery, but usually in patients with sustained ventricular arrhythmias.

Viral Myocarditis

- Commonest myocarditis; Coxsackie B virus being the most common virus
- Preceding upper respiratory illness
- Virus may be isolated from stools, pharyngeal washings or other body fluids
- Rising titres of specific antibodies in the blood
- Treatment—as above
- Usually a self-limited disease, but may progress to a chronic form

Q. Define cardiomyopathy. How do you classify cardiomyopathies?

Definition

- Cardiomyopathies are diseases that involve the myocardium primarily and are NOT as a result of hypertension, congenital heart diseases, valvular heart diseases, coronary heart disease, pericardial diseases or pulmonary diseases.
- The term "ischaemic cardiomyopathy" is frequently used but it is not a cardiomyopathy as the primary involvement is that of coronary arteries and not the myocardium.

Classification

- Cardiomyopathies are classified into three major groups based on the abnormalities of structure and function.
- The salient features of the three major groups are summarised in the information box below.

Type	Structural abnormality	Functional abnormality	Dysfunction
• **Dilated/congestive**	Enlargement of ventricle	Poor ventricular contraction	Systolic dysfunction
• **Restrictive/obliterative**	Small ventricle with "stiff wall"	Impairment of ventricular filling	Diastolic dysfunction
• **Hypertrophic**	Hypertrophy of left ventricle which may be generalised, but usually involving the upper portion of interventricular septum predominantly	Impairment of ventricular filling; Impairment of left ventricular ejection due to outflow tract obstruction (in 25%)	Predominantly diastolic dysfunction

Q. What are the causes, clinical features, salient investigations and treatment of dilated cardiomyopathy (congestive cardiomyopathy)?

Features

- In dilated cardiomyopathy there is enlargement of the ventricle and impairment of ventricular contraction, often affecting both ventricles.

Common Causes of Dilated Cardiomyopathy

Inflammatory
- Post-infective
- Autoimmune diseases (SLE, systemic sclerosis, dermatomyositis)

Nutritional
- Thiamine deficiency
- Selenium deficiency

Endocrine
- Diabetes mellitus
- Thyrotoxicosis
- Hypothyroidism

Haematological
- Sickle cell anaemia

Peripartum

Tachycardia-mediated cardiomyopathy

Toxic
- Alcohol
- Cocaine
- Adriamycin
- Trastuzumab
- Cyclophosphamide

Infiltrative
- Haemochromatosis

Neuromuscular
- Muscular dystrophies
- Friedreich's ataxia
- Myotonic dystrophy

Metabolic
- Glycogen storage disease

Idiopathic

Note: Some diseases can produce combined types of cardiomyopathies.

Clinical Features

Symptoms

- Symptoms of progressive left-sided and later right-sided heart failure
- Sudden death is common (due to arrhythmia)
- Symptoms of systemic embolisation of left ventricular mural thrombi or pulmonary embolism due to embolism of right ventricular thrombi

Signs

- Narrow pulse pressure and raised jugular venous pressure
- Cardiomegaly

- Signs of heart failure
- Third and fourth heart sounds
- Mitral and/or tricuspid regurgitation (functional)
- Arrhythmias are very common

Investigations

- Chest radiography
  - Left ventricular enlargement or generalised cardiomegaly
  - Evidence of pulmonary venous hypertension and interstitial or alveolar oedema
- Electrocardiogram
  - Non-specific ST–T wave changes
  - Sinus tachycardia, atrial fibrillation or other arrhythmias
  - Atrial and ventricular enlargement
- Echocardiography can confirm the diagnosis. It reveals dilatation of left and/or right ventricle with poor global contraction function.
- Circulating levels of BNP are elevated.
- Angiography should be performed in older patients to exclude CAD.

Treatment

- Avoid strenuous exertion
- Treatment of heart failure (diuretics, ACE inhibitors, and β-blockers)
- Additional vasodilators include nitrates, amlodipine and hydralazine
- Use of aldosterone antagonists (spironolactone and eplerenone)
- Inotropes (digoxin, dopamine and dobutamine) in severe cases not responding to other medicines
- Anticoagulation to prevent embolism
- Prevention and treatment of arrhythmias (antiarrhythmic drugs, permanent pacemaker, implantable cardioverter defibrillator)
- Cardiac resynchronisation therapy in patients who have evidence of dyssynchrony and who have NYHA class III or IV heart failure and continued symptoms despite maximal medical therapy
- Left ventricular assist devices
- Cardiac transplantation

Alcoholic Cardiomyopathy

- Develops in individuals who consume large quantities (>90 g/day) of alcohol over several years
- Presentation and treatment similar to idiopathic DCM
- Another form of alcoholic cardiotoxicity (not cardiomyopathy) is "holiday heart syndrome" that appears after a drinking binge. The name is derived from the fact that episodes are initially observed more frequently after weekends or public holidays, though in many patients, there is no such relation. Presentation is with recurrent supraventricular (particularly atrial fibrillation) and ventricular arrhythmias.

Peripartum Cardiomyopathy

- Usually occurs in multiparous females after the age of 30 years. Other risk factors include hypertension, pre-eclampsia and multiple (twins or triplets) gestations.
- Defined as:
  - Features of dilated cardiomyopathy during the last month of pregnancy or within 6 months of delivery
  - Absence of a demonstrable cause for the cardiac failure
  - Absence of demonstrable heart disease before the last month of pregnancy
  - Documented systolic dysfunction
- Management is similar to patients with dilated cardiomyopathy. Pregnancy must be avoided as the condition may recur.

Q. Discuss the causes, clinical features, investigations and treatment of restrictive cardiomyopathy (obliterative cardiomyopathy).

Features

- Ventricular walls are excessively stiff resulting in impairment of ventricular filling in diastole (abnormal diastolic function). This leads to high atrial pressures with atrial hypertrophy, dilatation and later atrial fibrillation.

Common Causes of Restrictive Heart Disease

Primary	Infiltrative
• Endomyocardial fibrosis	• Amyloidosis
• Eosinophilic endomyocardial disease	• Sarcoidosis
• Idiopathic	• Neoplasm
Metabolic	• Haemochromatosis
• Glycogen storage disease	**Mediastinal radiation**
• Fabry's disease	

Clinical Features

- Clinical features are similar to that of constrictive pericarditis (see later).
- Exercise intolerance and dyspnoea are the most common symptoms.
- Systemic embolism occurs in nearly 25% cases.
- Jugular venous pressure may be elevated with diastolic collapse and positive Kussmaul's sign.
- Peripheral oedema, ascites and enlarged tender liver.
- In most patients there is mild cardiac enlargement, the cardiac apex is easily palpable and a mitral regurgitation murmur may be heard (these features are not seen with constrictive pericarditis).
- Heart sounds are soft.
- Third and fourth heart sounds may be heard.

Investigations

- Electrocardiogram
  - Non-specific ST–T wave changes
  - Low voltage
  - Arrhythmias
- Chest radiography shows mild cardiomegaly without any pericardial calcification.
- Echocardiography can confirm the diagnosis. It shows symmetrically thickened left ventricular walls.
- Cardiac MRI and CT typically show symmetrically thickened left ventricle wall, and normal or slightly reduced ventricular volumes and systolic function. These help in excluding constrictive pericarditis by showing normal pericardium (in constrictive pericarditis CT or MRI may show thickened pericardium with or without calcification).
- Cardiac catheterisation shows increased ventricular filling pressures with typical dip-and-plateau pattern. In contrast to equalisation of left- and right-sided diastolic pressures in constrictive pericarditis, left and right ventricular diastolic pressures are separable by more than 5 mmHg in restrictive cardiomyopathy due to unequal involvement and compliance of two ventricles.

Treatment

- Mainly symptomatic (careful use of diuretics)
- Chronic anticoagulation
- Excision of fibrotic endocardium (in endomyocardial fibrosis)
- Cardiac transplantation

Q. Discuss the clinical features, investigations and treatment of hypertrophic cardiomyopathy (HCM).

Q. Briefly outline hypertrophic obstructive cardiomyopathy (HOCM) and idiopathic hypertrophic subaortic stenosis (IHSS).

Features

- There is left ventricular hypertrophy that may be generalised, but usually involving the interventricular septum predominantly. The upper portion of the interventricular septum is more hypertrophied (asymmetrical septal hypertrophy—ASH) and may result in left ventricular outflow tract obstruction (in 25%).
- Cases with outflow tract obstruction are referred to as hypertrophic obstructive cardiomyopathy (HOCM) and those without obstruction as HCM. However, since obstruction is dynamic, the term HOCM is not used now a days.
- The overall annual death rate in patients with HCM is estimated at ~ 1%/year, whereas that in patients with obstruction is ~ 2%/year.
- The disease is familial and transmitted as an autosomal dominant trait.

Clinical Features

- Many patients are asymptomatic.
- Family history of sudden death may be positive.
- Dyspnoea, fatigue, angina (due to ventricular hypertrophy which increases myocardial oxygen demand, particularly during exertion), syncope or near syncope.
- Sudden death during or after physical exertion.
- Arrhythmias are common.
- Rapidly rising carotid pulse ("jerky").
- Bisferiens pulse (two systolic peaks).
- Double apical impulse.
- Loud fourth heart sound.
- Harsh ejection systolic murmur best heard at the lower-left sternal border as well as at the apex due to left ventricular outflow tract obstruction. This murmur increases during standing and Valsalva manoeuvre (which reduce ventricular preload) but decreases during squatting and sustained hand grip (which increase afterload), and also by leg raising (which increases preload). This situation is in contrast to a murmur of aortic stenosis, in which these manoeuvres decrease the intensity of the murmur.
- Pansystolic murmur at mitral area due to mitral regurgitation.

Investigations

- Electrocardiogram shows left ventricular hypertrophy, and widespread deep and broad Q waves.
- Chest radiograph is normal or shows mild-to-moderate cardiac enlargement.
- Echocardiography is diagnostic. It may also show systolic anterior motion of anterior leaflet of mitral valve, which is a major contributor to left ventricular outflow tract obstruction and the accompanying mitral regurgitation.

Treatment

- β-blockers in angina and syncope. Treatment with β-blockers improves ventricular relaxation, increases diastolic filling time, and reduces susceptibility to ventricular and supraventricular arrhythmias.
- Amiodarone for controlling arrhythmias.
- Calcium channel blockers that do not have significant vasodilatory action are also beneficial because of their negative inotropic and chronotropic effects. They should not be used in presence of left ventricular outflow tract obstruction.
- If β-blockers alone are not sufficient, disopyramide (which also has a negative inotropic effect) along with β-blockers are helpful to reduce outflow tract obstruction.
- Surgical myotomy or myectomy of the hypertrophied septum.
- Digoxin, diuretics, nifedipine, nitrates and β-agonists should be avoided since they increase outflow tract obstruction.
- Implantable cardioverter-defibrillator in high-risk patients (cardiac arrest survivors, spontaneous sustained or non-sustained ventricular tachycardia, family history of premature sudden death, unexplained syncope, left ventricular thickness ≥30 mm and abnormal blood pressure during exercise).
- Septal alcohol ablation is being increasingly used.
- Evaluation of family members.

Q. Discuss the aetiology, clinical features, investigations and management of acute pericarditis.

- Acute pericarditis is defined as an acute inflammatory disease of pericardium.

Aetiology

Common causes	Less common causes
- Tuberculosis - Viral—Coxsackie B virus, mumps, varicella, rubella - Post-myocardial infarction syndrome - Connective tissue diseases—SLE, rheumatoid arthritis, systemic sclerosis - Acute myocardial infarction - Idiopathic (majority)	- Rheumatic fever - Uraemia - Malignant disease - Hypothyroidism - Secondary to bacterial infections (including pneumonia) - Trauma and post-surgical - Radiation therapy - Drugs—Hydralazine, procainamide, cytotoxics, phenytoin, penicillin, anticoagulants

Classification

- Depending on the underlying cause the inflammatory response in pericarditis may produce serous fluid, pus or dense fibrinous material.
- Pericarditis may be classified as acute (<6 weeks), subacute (6 weeks to 6 months) or chronic (>6 months) depending on the duration.

Clinical Features

- Pericardial pain, pericardial friction rub and pericardial effusion with or without cardiac tamponade and pulsus paradoxus (paradoxical pulse) are the cardinal clinical manifestations of acute pericarditis.
- Non-specific prodrome of fever, malaise and chest pain occurs in viral or idiopathic pericarditis.
- Myocarditis may be associated with pericarditis. Features of myocarditis have been discussed previously.
- Recurrence in about 30% cases.

Pericardial Pain

- It is characteristically retrosternal in location, radiating to shoulders and neck. Radiation to one or both trapezius muscle ridges is suggestive of pericardial pain.
- Pain may be steady and constrictive or worsened by inspiration, coughing and change of body position ("pleuritic").
- It may be relieved by sitting up and leaning forward.

Pericardial Friction Rub

- Pericardial friction rub is a superficial scratching sound, best heard to the left of sternum, often better heard (louder) by applying firm pressure with the diaphragm.
- It is usually better heard with the patient sitting upright and leaning forward.
- Pericardial friction rub has a to-and-fro, leathery character. It is often transitory, disappearing and re-appearing repeatedly.
- Classic pericardial rub has three phases that correspond to movement of heart during three phases of cardiac cycle: (i) Atrial systole, (ii) ventricular systole and (iii) rapid ventricular filling during early diastole. However, some rubs are present in only one (monophasic) or two (biphasic) components of cardiac cycle.

Pericardial Effusion and Cardiac Tamponade

- A detailed account of the clinical manifestations of pericardial effusion and cardiac tamponade is given later.

Pulsus Paradoxus

- Pulsus paradoxus (paradoxical pulse) is characterised by weakness or disappearance of arterial pulse during inspiration.

Investigations

- Non-specific elevation in total leucocyte count and ESR
- Normal cardiac enzymes (CPK-MB, and troponin T) unless associated myocarditis present
- Autoantibodies if connective tissue diseases are suspected clinically
- Electrocardiogram
  - Widespread ST segment elevation in multiple leads (particularly leads I, II, aVL, aVF and V_1–V_3), with concavity upwards ("smiling face"); ST depressed in aVR and sometimes in V_1; depression of PR segment (Stage 1).
  - Subsequently, ST and PR segments normalise (Stage 2).
  - T waves becomes inverted later when ST segments become normal (Stage 3).
  - In the final stage ECG becomes normal (Stage 4).
  - QRS voltage is reduced with pericardial effusion.
  - Electrical alternans in large pericardial effusion.

Comparison of ECG Changes in Acute Pericarditis and Acute ST-Elevation Myocardial Infarction

ECG finding	Acute pericarditis	Acute ST-elevation MI
- ST-segment shape	- Concave upward	- Convex upward
- Reciprocal ST-segment changes	- Absent	- Present
- Location of ST-segment changes	- Diffuse (except aVR and V_1)	- Depend on coronary artery involved

ECG finding	Acute pericarditis	Acute ST-elevation MI
• Q waves	• Absent	• Present
• PR-segment depression	• Present	• Absent
• Concomitant presence of ST and T changes	• Absent (T wave inversion occurs after ST segments have normalised)	• Present

- Chest radiography
  - Without an effusion, chest radiograph is normal.
  - Rapid increase in the size of the cardiac shadow occurs in pericardial effusion.
  - "Pear-shaped" or "water-bottle" appearance of heart in pericardial effusion.
- Echocardiography can confirm the pericardial effusion.
- Cardiac MRI may be done to look for pericardial inflammation and also involvement of myocardium.
- Diagnostic paracentesis in pericardial effusion (refer later). It is indicated when the patient has tamponade or a large or symptomatic effusion despite medical therapy, and in cases in which tuberculous, purulent or neoplastic pericarditis is highly suspected.

Treatment

- Rest and avoidance of physical activity
- Hospitalisation if high-risk features (i.e. presence of specific, non-idiopathic, non-viral aetiology or high likelihood of complications) present:
  - Fever (temperature >38°C)
  - Leucocytosis
  - Large pericardial effusion (echo-free space >20 mm)
  - Cardiac tamponade
  - Acute trauma
  - Immunosuppressed state
  - Concurrent oral anticoagulation
  - Elevated troponin levels
  - Recurrent pericarditis
  - Lack of response to NSAIDs after 1 week of therapy.
- Aspirin 600 mg 4 hourly or ibuprofen 300–800 mg 8 hourly for relief of pain and reduction in inflammation in idiopathic or viral pericarditis. Can be continued till pain and pericardial effusion disappear and ESR, CRP normalise (usually 7–10 days) followed by tapering over next few weeks.
- Indomethacin 25 mg 8 hourly is a more potent anti-inflammatory drug. Should be avoided in elderly patients as it can reduce flow in the coronaries.
- Colchicine (0.5 mg twice a day) alone or in addition to NSAIDs is effective for initial attack and prevention of recurrences.
- Corticosteroids (10–30 mg/day for 2–4 weeks) in selected cases (pericarditis associated with uraemia and connective tissue diseases) or those who do not respond to NSAIDs. This is followed by tapering over next few months. However, use of corticosteroids in viral aetiology is associated with an increased risk of pericarditis recurrence.
- Treatment of the underlying cause.

Q. Discuss the aetiology, clinical features, investigations and management of pericardial effusion.

- Pericardial effusion may be transudate (hydropericardium), exudate, pyopericardium or haemopericardium.
- Pericardial effusion is usually associated with one or more manifestations of pericarditis (refer before).
- Causes of pericardial effusion are the same as that for pericarditis (refer before).
- Effusions that develop slowly can be remarkably asymptomatic. If it develops over a short period, it may lead to cardiac tamponade.

Clinical Signs

- Apical impulse may not be palpable, but sometimes palpable well medial to the left border of cardiac dullness.
- Increase in cardiac dullness on percussion.

- Heart sounds are faint or muffled. A pericardial friction rub may or may not be audible.
- In a large effusion there may be an area of dullness and tubular breathing at the angle of left scapula, resulting from compression of lung (Ewart's sign).

Investigations

- Chest radiography
  - Enlarged cardiac silhouette
  - "Water-bottle" appearance of heart shadow
  - Lucent pericardial fat lines
- Fluoroscopy shows diminished ventricular pulsations.
- Electrocardiogram
  - Electrical alternans and low-voltage QRS complexes
  - May show signs of pericarditis (refer above)
- Echocardiography can confirm the diagnosis
- Diagnostic paracentesis (pericardiocentesis) and analysis of fluid. The most serious complications of pericardiocentesis are laceration and perforation of myocardium and coronary vessels. In addition, patients can experience air embolism, pneumothorax, arrhythmias (usually vasovagal bradycardia), and puncture of the peritoneal cavity or abdominal viscera. Important investigations on pericardial fluid include:
  - Cell counts, protein, glucose and LDH to differentiate exudates from transudates
    - Protein >3.0 g/dL (or fluid:serum ratio >0.5)
      - LDH >200 mg/dL (or serum:fluid ratio >0.6)
      - Glucose >two-third serum glucose in transudates
      - White cell count is high in inflammatory diseases (bacterial and rheumatologic) and low in myxoedema
  - Cholesterol is high (>100 mg/dL) in bacterial and malignant pericardial fluids
  - Gram's stains and AFB stain
  - Cytology for malignant cells
  - Adenosine deaminase (ADA) and interferon-γ in tuberculosis
  - Mycobacterium culture or radiometric growth detection (e.g. BACTEC)
  - PCR analyses for tuberculosis and viruses
  - Tumuor markers (carcinoembryonic antigen, and cytokeratin 19 fragment)
- Cardiac catheterisation and angiocardiography are rarely needed
- Thoracic and abdominal CT to rule out presence of lymphadenopathies and masses

Treatment

- Therapeutic paracentesis with aspiration of effusion in selected cases. May be done using a pig-tail catheter insertion under echocardiogram.
- Anti-inflammatory drugs like aspirin or indomethacin.
- Treatment of underlying cause.
- In neoplastic conditions causing recurrent effusion, intrapericardial instillation of chemotherapeutic agents may be done.

Q. Give a brief account of tuberculous pericarditis.

- Usually secondary to pulmonary tuberculosis.
- Insidious onset and slow progression with weight loss, fever and fatigue.
- Clinical examination reveals a pericardial effusion (refer before).
- Associated pleural effusion is very common.
- Natural history of tuberculous pericarditis is that of a chronic pericardial effusion with eventual thickening of pericardium, later leading to constrictive pericarditis.

Investigations

- Chest radiograph shows a "water-bottle" configuration of heart.
- Echocardiography is important to confirm pericardial effusion. It may show cardiac tamponade, calcification of pericardium or features of constrictive pericarditis.

- Diagnosis is confirmed by aspiration of the fluid (which is an exudate with low sugar and elevated ADA), direct examination and culture for tubercle bacilli and PCR for *M. tuberculosis*.
- Other investigations include chest radiograph for pulmonary tuberculosis and tuberculin skin test.
- Pericardial biopsy is rarely needed for confirmation of diagnosis.

Treatment

- Antituberculous chemotherapy for 6–9 months.
- Corticosteroids will reduce the incidence of constrictive pericarditis.
- Therapeutic aspiration (rarely) to relieve symptoms.
- Balloon pericardiotomy or pericardiectomy may be required at a later stage if constrictive pericarditis develops.

Q. Discuss the causes, clinical features, investigations and treatment of cardiac tamponade.

- Cardiac tamponade results from the accumulation of fluid in the pericardium in an amount sufficient to cause compression of the heart and impairment of diastolic filling.
- The minimum amount of fluid required for tamponade depends on the speed of accumulation (about 250 mL in rapidly developing effusions and more than 2000 mL in slowly developing effusions).
- Clinical features result from fall in cardiac output and systemic venous congestion.

Aetiology

- Pericardial effusion (refer before)
- Haemopericardium (anticoagulants, thrombolytics, recent cardiac surgery, indwelling catheters, and blunt trauma chest)

Clinical Features

- Dyspnoea and orthopnoea
- Substernal chest discomfort radiating to neck and jaw
- Right upper quadrant pain and pedal oedema in slowly developing cardiac tamponade (subacute tamponade)
- Tachycardia
- Pulsus paradoxus or paradoxical pulse is the hallmark of tamponade
- Hypotension
- Raised jugular venous pressure with prominent *x* descent but absence or attenuation of *y* descent
- Increase in cardiac dullness to percussion
- Normal respiratory sounds
- Faint heart sounds; pericardial rub uncommon
- Tender hepatomegaly
- Raised JVP, hypotension and muffled heart sounds constitute Beck's triad
- Kussmaul sign uncommon (see constrictive pericarditis)

Investigations

- Chest radiography shows clear lung fields and normal or enlarged cardiac silhouette depending on rate of accumulation of pericardial fluid. Rapid accumulation of small amount of pericardial fluid is sufficient to produce features of tamponade (acute tamponade) but without cardiac enlargement on chest radiograph.
- Diminished cardiac pulsations on fluoroscopy.
- Electrocardiogram might show sinus tachycardia, reduction in QRS voltage, non-specific ST–T changes and electrical alternans (alteration of QRS complex amplitude or axis between beats).
- Echocardiography can confirm the diagnosis by showing characteristic swinging motion of the heart, or diastolic collapse of right atrium, right ventricle and left atrium.

Management

- Emergency pericardiocentesis.
- In hypotensive patients volume expansion with saline, blood, plasma and dextran can be used as a temporary measure.

- Positive-pressure mechanical ventilation should be avoided in acute tamponade because it further reduces cardiac filling.
- Treatment of underlying cause.

Q. Describe chronic pericarditis.

- Chronic (>6 months) pericarditis includes effusive (inflammatory or hydropericardium in heart failure), adhesive and constrictive forms.
- Important causes include tuberculosis, histoplasmosis, toxoplasmosis, myxoedema, autoimmune diseases and systemic diseases.
- Symptoms are usually mild (chest pain, palpitations, and fatigue), and are related to degree of cardiac compression and pericardial inflammation.
- Treatment includes management of underlying cause and pericardiocentesis. For frequent and symptomatic recurrences balloon pericardiotomy or pericardiectomy may be done.

Q. Discuss the aetiology, clinical features, investigations and management of chronic constrictive pericarditis.

Q. Describe in brief about Kussmaul's sign.

- The pericardium becomes gradually fibrosed, thickened and inelastic. It acts as a rigid case, encasing the heart. It interferes with the diastolic relaxation of heart and hence ventricular filling. Hence, the inflow to the heart is reduced that is more during inspiration. The net result is a reduction in cardiac output and elevation of systemic venous pressure.

Aetiology

- Tuberculosis (commonest)
- Haemopericardium and cardiac surgery
- Mediastinal irradiation
- Rheumatoid arthritis and systemic lupus erythematosus
- Uraemia
- Asbestosis
- Acute pericarditis (rare)
- Malignancy (rare)

Clinical Features

- Clinical features result from reduced cardiac output and elevated systemic venous pressure.
- Weakness, fatigue, weight loss and anorexia.
- Patient appears emaciated with a protuberant abdomen.
- Pulse is of low volume and rarely pulsus paradoxus may be present.
- Neck veins are distended (engorged) with a sharp y descent, a deep y trough and rapid ascent to baseline.
- "Kussmaul's sign" may be positive. This is an increase in the height of jugular venous pulsations (and hence a rise in jugular venous pressure) during inspiration.
- Atrial fibrillation may be present.
- Apical impulse may not be palpable (easily palpable in patients with restrictive heart disease).
- Heart sounds may be muffled.
- An early diastolic sound, "pericardial knock" may be audible (occurs 0.09–0.12 second after A_2).
- Mitral regurgitation murmur is not heard (may be heard in patients with restrictive heart diseases).
- Congestive hepatomegaly.
- Ascites is more common, early and severe than peripheral oedema.
- Protein-losing enteropathy may develop producing hypoalbuminaemia.

Investigations

- Chest radiography
  - Heart size is normal or reduced (enlarged in patients with restrictive heart diseases).

- Pericardial calcification (absent in patients with restrictive heart diseases), best seen from a lateral view and located over right ventricle and diaphragmatic surface of heart.
- Fluoroscopy shows reduced cardiac pulsations.
- Electrocardiogram may show low voltage QRS complexes and non-specific T wave changes. Bundle branch block, ventricular hypertrophy, pathologic Q waves and impaired atrioventricular conduction are rarely seen; presence of these features strongly favour restrictive cardiomyopathy.
- Echocardiography can confirm pericardial thickening and calcification.
- Magnetic resonance imaging can confirm pericardial thickening.
- Cardiac catheterisation in selected patients.
  - Elevation and near equalisation of diastolic pressures in right atrium, right ventricle and pulmonary wedge pressure, which corresponds to left heart diastolic pressure.
  - Rapid *y* descent in jugular venous pressure and plateau during right heart catheterisation (square-root sign).
  - Respiratory variation in filling of left and right ventricles (not present in patients with restrictive cardiomyopathy).

Treatment

- Pericardiectomy (resection of the pericardium) is the only definitive treatment.

Q. Enumerate the common congenital heart diseases seen in adults.

Acyanotic congenital heart diseases	Cyanotic congenital heart diseases
- Ventricular septal defect	- Tetralogy of Fallot
- Atrial septal defect	- Transposition of great arteries
- Patent ductus arteriosus	
- Pulmonary stenosis	
- Aortic stenosis	
- Coarctation of aorta	

Q. Discuss the clinical features, investigations, complications and management of coarctation of aorta (COA).

Q. Explain briefly about Suzman's sign and radiofemoral delay.

- Coarctation of the aorta (COA) is a narrowing of the lumen of aorta. It can occur anywhere from distal part of arch of aorta to bifurcation of abdominal aorta, but it is commonly located immediately below the origin of the left subclavian artery.

Clinical Features

- More common in males. Commonly associated with bicuspid aortic valve (in 70%), Berry aneurysms in the circle of Willis (10%) and Turner's syndrome. Other associated lesions include ventricular septal defect and patent ductus arteriosus.
- Commonly diagnosed during workup for hypertension in adults.
- Minor symptoms include headache and epistaxis (due to hypertension), and leg fatigue or claudication (from decreased circulation in the lower part of body).
- Major symptoms are the symptoms related to four major complications:
  - Congestive heart failure
  - Infective endocarditis
  - Cerebral haemorrhage due to rupture of Berry aneurysm
  - Rupture or dissection of aorta
- Recurrent episodes of haematemesis and melaena are harbingers of impending rupture.
- Most patients with significant coarctation who do not undergo surgery die before the age of 40 years due to complications.

Coarctation of the aorta
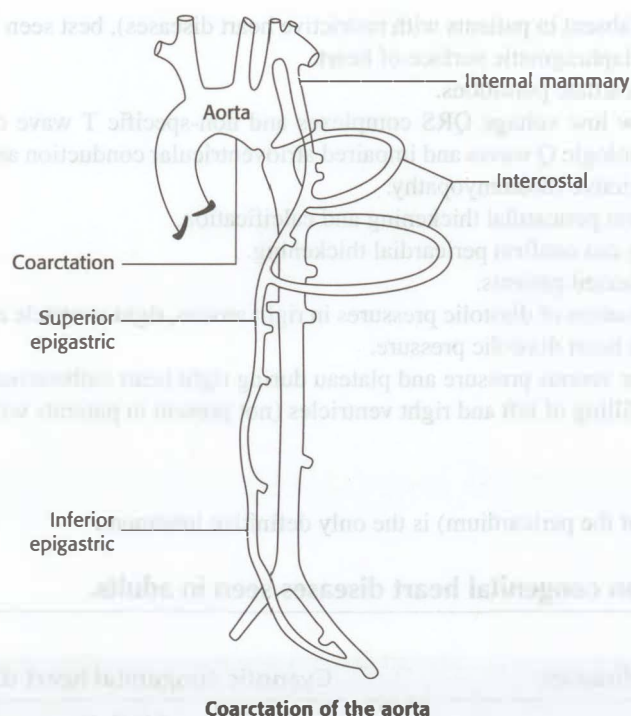
Signs

- Lower segment of the body may be underdeveloped
- Hypertension in the upper limbs with low or normal pressure in lower limbs (difference >20 mmHg)
- Weak and delayed femoral pulses (radiofemoral delay)
- Prominent pulsations in the neck
- "Suzman's sign" is dilated, tortuous, pulsatile, collateral arteries seen around the scapulae and intercostal regions in the back. It is better seen with the patient bent forwards and hands hanging down
- "Cork-screw" shaped retinal arteries
- Heaving apical impulse
- Aortic ejection sound if associated with bicuspid aortic valve

Murmurs in Coarctation of Aorta (COA)

- Ejection systolic murmur (ESM) over the spine from coarctation itself
- Systolic or continuous murmurs over lateral thoracic wall, arising from collaterals
- Ejection systolic murmur or early diastolic murmur (from aortic regurgitation) in the aortic area, from the associated bicuspid aortic valve

Investigations

- Electrocardiography, echocardiography, radiological studies and angiography can confirm the diagnosis.

Radiological Features of Coarctation of Aorta

- "Rib notching" or "Dock's sign" is the notching of the under surfaces of posterior ribs, extending from third to ninth ribs. It may be unilateral or bilateral, and is seen only after the age of 6 years. Occurs due to dilated collaterals pressing on the lower part of ribs
- "Poststenotic dilatation" is the dilatation of the aorta distal to coarctation
- "3 sign" is a combination of dilated pre-stenotic aorta and left subclavian artery above, stenosed, coarcted segment in the middle and dilated post-stenotic aorta below
- "E sign" is seen on the lateral view on a barium swallow. This results from the dilated prestenotic aorta and left subclavian artery and dilated post-stenotic aorta indenting the barium filled oesophagus

- CT and MRI to look for aortic aneurysm and coarctation.
- Cardiac catheterisation to assess associated cardiac lesions.

Complications

- Hypertension
- Left ventricular failure
- Cerebral aneurysm and haemorrhage
- Aortic dissection and rupture of aorta
- Infective endocarditis at the site of coarctation, bicuspid aortic valve or collateral channels
- Persistent renal damage if surgery is delayed

Treatment

- Treatment of hypertension and congestive heart failure. Avoid ACE inhibitors and angiotensin II receptor antagonists as they may result in inadequate lower-body perfusion and may precipitate renal failure.
- Surgical correction (hypertension persists in many patients even after surgery).
- Endovascular stenting for isolated coarctation of aorta (without other cardiac lesions).

Q. Discuss briefly the haemodynamics, clinical features, investigations, complications and management of persistent ductus arteriosus (patent ductus arteriosus—PDA).

Q. Give a brief account of differential cyanosis.

Aorta

Pulmonary artery

Persistent ductus arteriosus (PDA)
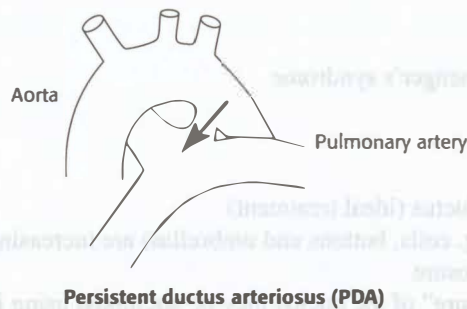
- Ductus arteriosus is a vessel leading from the bifurcation of the pulmonary artery to the aorta just distal and opposite to the origin of left subclavian artery. This is functional in foetus and diverts desaturated blood from main pulmonary artery into the descending aorta and placenta for oxygenation. It closes by birth due to post-natal drop in circulating prostaglandin E2 levels as well as rise in systemic oxygen tension.
- Persistence of the patency of this is known as patent ductus arteriosus (PDA).
- Higher incidence in premature newborns and those born at high altitude.
- Maternal rubella in first trimester predisposes to persistent ductus arteriosus.

Haemodynamics

- Since the pressure in the aorta is higher than in the pulmonary artery (both during systole and diastole) there will be a continuous flow of blood from aorta to pulmonary artery (L → R shunt) in both systole and diastole. When pulmonary hypertension develops, this blood flow diminishes initially in diastole. Later, with the development of Eisenmenger's syndrome (see later), the blood flow is reversed (R → L shunt). Now, the blood flows from pulmonary artery to aorta (i.e. reversal of the shunt).

Clinical Features

- More common in females.
- Retardation of growth and development in children.
- Dyspnoea.
- Collapsing pulse.
- Apex beat is shifted down and out and hyperdynamic in character.

- Continuous thrill at the upper-left sternal edge.
- First heart sound is loud (due to loud mitral component).
- Continuous "machinery murmur" with late systolic accentuation at the upper left sternal edge. Multiple ejection clicks are heard within this murmur. It should be distinguished from "to-and-fro" murmur that is a combination of an ejection systolic murmur and an early diastolic decrescendo murmur (for example aortic stenosis and insufficiency). There is a definite gap between the end of the ejection murmur and the second heart sound in "to-and-fro" murmur.
- Left ventricular third heart sound and a mid diastolic flow murmur at the apex with large L → R shunt.
- With the development of pulmonary hypertension signs of pulmonary hypertension develop.
- With the development of Eisenmenger's syndrome, shunt reverses (R → L), and central cyanosis and clubbing develop. Cyanosis and clubbing develop only in lower limbs but not in the upper limbs (differential cyanosis). The continuous murmur becomes quieter, confined to systole and later disappears.

Investigations

- Chest radiography, electrocardiogram, echocardiography and if necessary cardiac catheterisation.
- Electrocardiogram frequently shows left atrial enlargement. Others include features of left ventricular hypertrophy and biventricular hypertrophy.
- Chest X-ray shows increased vascular markings (plethoric fields) along with enlarged left atrium and ventricle.
- Echocardiogram and colour Doppler shows PDA as well as amount of blood flow through the ductus arteriosus.

Complications

- Cardiac failure
- Infective endocarditis
- Paradoxical embolism
- Pulmonary hypertension and Eisenmenger's syndrome
- Rupture of the ductus

Management

- Surgical ligation or division of the ductus (ideal treatment)
- Transcatheter occluding devices (e.g. coils, buttons and umbrellas) are increasingly used.
- Video-assisted thoracoscopic clip closure
- In premature babies a "medical closure" of the ductus may be attempted using indomethacin (it inhibits prostaglandin synthesis). However, it may produce necrotising enterocolitis and renal insufficiency. Use of ibuprofen has been found to be as effective as indomethacin with lower incidence of adverse effects. These are rarely effective in full term babies.

Q. What is reversed differential cyanosis?

- Cyanoses of upper limbs exceeds that of the lower limbs.
- Seen in transposition of great arteries (blood from right ventricle ejected into the aorta reaches the upper limbs and head, blood from left ventricle is ejected into pulmonary artery and reaches the lower limbs via PDA).

Q. Discuss briefly the haemodynamics, clinical features, investigations, complications and management of atrial septal defect (ASD).

Q. Explain briefly about Lutembacher's syndrome.

Q. What is meant by patent foramen ovale?

Types

- Atrial septal defect (ASD) is a defect in the interatrial septum. Based on the location of the defect it can be classified into three types:
  - Ostium secundum type (commonest) that involves the fossa ovalis in the mid-septal region. 20% of these cases are associated with mitral valve prolapse. This should not be confused with patent foramen ovale that is normal variant and not a true septal defect.
  - Ostium primum type (rare)—It occurs near AV valves. The AV valves may also be deformed (AV septal defects or AV canal defects or endocardial cushion defects).

- Sinus venosus type (rare)—It occurs high in the atrial septum near the entry of superior vena cava and is almost always associated with partial anomalous pulmonary venous return (to SVC or right atrium).
- Lutembacher's syndrome is a rare combination of ASD and rheumatic mitral stenosis.

Patent Foramen Ovale

- Patent foramen ovale may be seen in >25% of adult population and is haemodynamically insignificant.
- Usually asymptomatic but is associated with paradoxical emboli and increased incidence of embolic stroke.
- Other complications include decompression syndrome, orthodeoxia–platypnoea syndrome (dyspnoea and arterial desaturation induced by upright posture and relieved by recumbence) and peripheral embolism.
- An incidentally detected patent foramen ovale generally requires no follow-up or treatment. If an embolic stroke has occurred and is likely caused by patent formaen ovale, medical therapy with antiplatelet agents or anticoagulation, and surgical or percutaneous closure of the defect are the options.

Haemodynamics

- In ASD blood is shunted from left atrium to right atrium and then to right ventricle. The right ventricular output and hence pulmonary blood flow is markedly increased. This leads to progressive enlargement of right atrium, right ventricle and pulmonary arteries. Eventually, pulmonary hypertension appears with reversal of the shunt (R → L shunt).

Clinical Features

- Commonest congenital heart disease seen in adults. More common in females
- Many asymptomatic and diagnosed on routine examination
- Palpitations and fatigue
- Recurrent respiratory infections
- Retarded growth and development
- Dyspnoea, cardiac failure and arrhythmias like atrial fibrillation occur late in the course of illness
- Occasionally, a paradoxical embolism

Signs

- Hyperdynamic precordium
- Visible and palpable pulmonary artery pulsations in the second left intercostal space
- Left parasternal heave
- Systolic thrill over the pulmonary area (uncommon)
- S_1 is loud (due to accentuated tricuspid component of first sound)
- Second heart sound is widely split and fixed in relation to respiration
  - "Widely split" because the pulmonary valve closure is delayed by the larger volume of blood to be ejected by the right ventricle.
  - "Fixed split" since the volume of blood ejected across the pulmonary valve is the same in inspiration and expiration.
- Ejection systolic murmur over the pulmonary area due to increased flow across the pulmonary valve.
- Mid-diastolic rumbling murmur (flow murmur) over the tricuspid area due to increased flow across the tricuspid valve.
- A pansystolic murmur of tricuspid regurgitation produced by dilatation of right ventricle.
- A pansystolic murmur of mitral regurgitation is characteristic of primum ASD.
- No audible murmur occurs secondary to flow across ASD.
- With the onset of pulmonary hypertension signs of pulmonary hypertension develop.
- With the development of Eisenmenger's syndrome, central cyanosis and digital clubbing develop. Both pulmonary and tricuspid murmurs decrease in intensity and later disappear. Development of pulmonary hypertension and reversal of the shunt (Eisenmenger's syndrome) are late events in ASD (usually by third and fourth decade of life).

Investigations

- Chest radiography, electrocardiogram, echocardiography and if necessary cardiac catheterisation.
- Chest radiography reveals a prominent pulmonary artery and increased pulmonary vascular markings or pulmonary plethora (seen in all L → R shunt). Cardiomegaly may occur due to right ventricular enlargement. A small aortic knuckle is characteristic, which occurs due to chronically low systemic cardiac output.
- The electrocardiogram shows right atrial enlargement (*P* pulmonale), mild right ventricular hypertrophy, right axis deviation and rSR' pattern (right bundle branch block) in the right chest leads in ostium secundum ASD. In ostium

primum ASD, ECG shows prolonged PR interval and left axis deviation with right bundle branch block. In sinus venosus type of ASD inverted P waves are seen in inferior leads.

- Echocardiogram reveals enlarged right ventricle with paradoxical septal motion, particularly well demonstrable on M-mode echocardiogram. By two-dimensional echocardiogram the defect can be clearly visualised.
- Cardiac MRI may be useful and may give the same type of information that echocardiography can provide. It provides assessment of right ventricular size and function.
- Cardiac catheterisation is rarely required; most catheterisations are done with the intention to close the defect percutaneously. In selected patients, angiography is done to delineate associated anomalies not shown by non-invasive imaging. When catheterisation is performed step-up in oxygen saturation is seen at the right atrial level.

Complications

- Congestive heart failure (in neonates)
- Paradoxical embolism (with right-to-left shunt)
- Atrial fibrillation
- Pulmonary hypertension (late)
- Eisenmenger's syndrome (very late)
- Infective endocarditis (extremely rare)

Management

- Prompt treatment of respiratory infections.
- Surgical closure of the defect in patients above 3 years of age, provided there are no signs of pulmonary hypertension and the pulmonary flow is 50% more than the systemic blood flow (Qp:Qs >1.5/1).
- A percutaneous transcatheter septal occluder may be used as an alternative to surgical closure for patients with ostium secundum type ASD.
- Uncorrected ASD does not require antibiotic prophylaxis for endocarditis unless other high-risk conditions are present (see "infective endocarditis").

Q. Discuss briefly the haemodynamics, clinical features, investigations, complications and management of congenital ventricular septal defect (VSD).

Q. Discuss briefly about Maladie de Roger.

- The interventricular septum has a membranous and a muscular portion. VSD implies a defect in the interventricular septum. Most of the VSDs are "perimembranous", i.e. at the junction of membranous and muscular portions. Muscular defect is uncommon.
- May be associated with ASD, PDA or pulmonic stenosis.
- Maladie de Roger—Small VSDs in muscular portion, presenting in older children as a loud pansystolic murmur without other haemodynamic changes. Such defects usually close spontaneously.

Haemodynamics

- The blood flows from the left ventricle to the right ventricle and then to the pulmonary artery. This ultimately results in a volume overload of the ventricles if the shunt is large. Pulmonary hypertension and reversal of shunt occur at a later stage.

Clinical Features

- Commonest congenital heart disease in paediatric age group. Detected due to presence of a murmur on routine examination.
- Clinical features depend on the size of the defect and magnitude of the shunt.
- Recurrent respiratory infections.
- Failure to thrive.
- Congestive heart failure.
- Hyperdynamic precordium.
- Apex beat is shifted down and out and is hyperdynamic in character.
- Systolic thrill at the third or fourth left intercostal space.
- Pulmonary component of second sound normal or increased, depending upon the degree of elevation pulmonary artery pressure.

- Harsh pansystolic murmur, best heard at the third or fourth left intercostal space, but radiating all over precordium. No consistent relationship of intensity of murmur with the size of the defect. If the defect is muscular, murmur may stop well before S_2 because the defect decreases in size or obliterates in the later part of systole.
- Left ventricular third heart sound and a mid diastolic rumbling murmur (flow murmur) at the apex due to increased flow across the mitral valve. Indicates pulmonary:systemic (Qp:Qs) blood flow ratio >2:1.
- Incidence of ventricular arrhythmias increased in VSD.
- With the development of pulmonary hypertension, signs of pulmonary hypertension appear. Later, with reversal of the shunt (Eisenmenger's syndrome) the murmur of VSD disappears, and central cyanosis and clubbing appear.

Investigations

- Chest radiography, electrocardiography, echocardiography, and if necessary, cardiac catheterisation.
- Chest X-ray shows cardiomegaly and increased pulmonary vascular markings if the shunt is large. Left atrial enlargement may also be noted.
- Electrocardiogram may be normal in small defects or may show evidence of left ventricular hypertrophy in small-to-moderate defects while it may show biventricular or right ventricular hypertrophy in moderate to large defects. Features of left atrial enlargement may also be seen. Another common finding is presence of intraventricular conduction defect or right bundle branch block.
- Echocardiography to assess location and size of VSD as well as blood flow across it. It can also define associated cardiac lesions.
- Cardiac catheterisation to assess pulmonary vascular resistance in complicated VSD.

Complications

- Congestive heart failure
- Pulmonary hypertension
- Eisenmenger's syndrome
- Right ventricular outflow tract obstruction
- Aortic regurgitation
- Infective endocarditis (rare)

Natural History

- Spontaneous closure in approximately 40% cases.
- Additional 25–30% of defects may become small enough not to require surgical intervention.
- Majority of defects close by age 2, most close by age 5–7 years.
- Pulmonary vascular obstructive disease may develop in 10%.
- Infundibular stenosis (Gasul's transformation) may occur in 8% of the defects. Though patient will require surgery, it prevents development of pulmonary vascular obstructive disease.
- Aortic insufficiency develops in approximately 5% of patients. This may either be related to prolapse of an aortic valve cusp into VSD or lack of support to the aortic root. This complication appears to occur more with advancing age.

Management

- Small VSDs with small shunts require no treatment as they are likely to close spontaneously.
- Operative correction is indicated in moderate to large defects with significant left-to-right shunt (pulmonary-to-systemic blood flow ratio >1.5:1.0). Also indicated after an episode of infective endocarditis irrespective of degree of shunting.
- Large VSDs with severe elevation of pulmonary resistance (irreversible pulmonary vascular obstructive disease) are not candidates for surgery. Symptomatic treatment and venesection for symptoms of polycythaemia should be undertaken. These patients may eventually become candidates for lung transplantation.

Q. What is Eisenmenger's syndrome? Discuss the clinical presentation of Eisenmenger's syndrome.

- Eisenmenger's syndrome is the consequence of the reversal of a left-to-right shunt to a right-to-left shunt. It occurs in patients with congenital heart diseases, especially PDA, VSD and ASD.
- Basically, (before the reversal of the shunt), in patients with L → R shunt (ASD, VSD, and PDA) the oxygenated blood from the left side of the heart gets mixed with the deoxygenated blood of the right side of the heart. Over a period of time pulmonary vascular disease sets in and pulmonary vascular resistance goes up, ultimately resulting in pulmonary hypertension.

- When pulmonary arterial pressure goes up (pulmonary hypertension) the pressure in the pulmonary circuit exceeds the pressure of systemic side. This results in an obligatory reversal of shunt, now from right side to left side (R → L shunt). This is termed Eisenmenger's syndrome.

Clinical Features

- Dyspnoea, cyanosis, fatigue, dizziness and syncope.
- Central cyanosis and clubbing occur from mixing of deoxygenated blood with oxygenated blood. It is generalised in ASD and VSD reversal, while it is differential (only lower limbs) in PDA with reversal.
- Conditions that cause systemic vasodilatation (e.g. fever, exertion, and hot weather) may exaggerate shunt from right-to-left, resulting in systemic desaturation.
- Signs of pulmonary hypertension and its sequelae (refer "pulmonary hypertension").
- S_2 is loud with palpable P_2:
  - S_2 fixed but narrowly split in ASD with reversal
  - S_2 single in VSD with reversal
  - S_2 mobile but narrowly split in PDA with reversal
- Eventually, patient dies of right heart failure. Other causes of death include pulmonary infections, infective endocarditis, severe haemoptysis, secondary erythrocytosis, pulmonary thrombosis with infarction, brain abscess, cerebral stroke and ventricular arrhythmias. These complications are uncommon in idiopathic pulmonary arterial hypertension.
- Survival is better in Eisenmenger's syndrome as compared to idiopathic pulmonary arterial hypertension.
- The characteristic murmurs of the underlying defect (ASD, VSD, and PDA) decrease in intensity, duration and finally disappear with the development of Eisenmenger's syndrome.

Treatment

- Surgery with correction of an underlying defect in early phase where pulmonary hypertension is due to increased volume load and not due to increased pulmonary vascular resistance.
- Vasodilator therapy using calcium channel blockers may be detrimental as systemic vasodilatation may further increase right-to-left shunt.
- Long-term oxygen inhalation may improve symptoms.
- Diuretics and digoxin may be helpful in a few patients.
- Phlebotomy in patients with hyperviscosity syndrome due to erythrocytosis with haematocrit >65%.
- The only curative treatment is heart–lung transplantation.
- Prostanoids (e.g. epoprostenol, iloprost, and treprostinil), endothelin receptor antagonists (e.g. ambrisentan, and bosentan) and phosphodiesterase-5 inhibitors (e.g. sildenafil, and tadalafil) may improve symptoms.

Q. Describe Fallot's tetralogy or Tetralogy of Fallot (TOF).

- It is the most common congenital cyanotic heart disease in adults. It consists of four features:
  - VSD (almost always large)
  - Right ventricular hypertrophy
  - Pulmonary stenosis, most commonly subvalvular or infundibular
  - Over riding aorta (biventricular connection of the aortic root)
- Presence of ASD along with TOF is known as pentalogy of Fallot.

Clinical Features

- Children at birth and early neonatal period are generally asymptomatic except for presence of cyanosis.
- Within a few weeks to months of birth children with TOF often develop dyspnoea, fatigue and hypoxic (cyanotic) spells on exertion (deepening of cyanosis with possible syncope).
- Cyanotic spells (tet spells) occur during feeding, crying, fever or exercise due to systemic vasodilatation producing increased right-to-left shunting across VSD. These factors also increase right ventricular obstruction. With progression of spell, metabolic acidosis develops that further reduces systemic resistance and increases pulmonary vascular resistance. This can result in sudden death. Squatting is common as it increases peripheral resistance, thereby reducing right-to-left shunting and increases systemic venous return.
- Adults tend to have growth retardation, fatigue and dyspnoea on exertion but cyanotic spells are not the usual features. Polycythaemia secondary to chronic hypoxia is common and can lead to thrombotic strokes.

- Examination shows clubbing, central cyanosis, parasternal heave, systolic thrill, single loud second heart sound (pulmonary component is too soft to be heard) and ejection systolic murmur in the second and third left intercostal spaces (due to pulmonary outflow obstruction). Intensity and duration of murmur is inversely proportional to severity of right ventricular outflow tract obstruction. Since VSD is large, its murmur is not heard.

Investigations

- Chest radiography shows a large right ventricle and a small pulmonary artery ("Coeur en Sabot" or "boot-shaped" heart—"boot" by enlarged right ventricle, and concavity by underdeveloped right ventricular outflow tract and main pulmonary artery). The lung fields are oligaemic.
- Right ventricular hypertrophy in the electrocardiogram.
- Echocardiography.
- Cardiac catheterisation is rarely needed as echocardiography is highly sensitive.

Complications

- Intravascular thrombosis due to polycythaemia resulting in cerebrovascular accidents and embolism
- Brain abscess
- Higher incidence of pulmonary tuberculosis
- Infective endocarditis

Treatment

- Complete correction in infants and children.
- Blalock–Taussig shunt (a shunt between a subclavian artery and pulmonary artery on the same side) in very young infants and premature babies in order to increase the blood supply to the lungs.
- Cyanotic spells are treated by:
  - Asking the patient to squat ("knee-to-chest" position).
  - Administering oxygen.
  - Intravenous fluids to increase venous return.
  - Administering morphine at a dose of 0.1 mg/kg intravenously to reduce release of catecholamines. This will increase period of right ventricular filling by decreasing heart rate and promote relaxation of infundibular spasm.
  - Administering propranolol at a dose of 0.01 mg/kg intravenously followed by oral dose of 3–5 mg/kg/day in divided doses. However, β-blockers can produce hypotension.
  - Ketamine (1–3 mg/kg IV) can also increase systemic vascular resistance and provide sedation.
- Antibiotic prophylaxis for endocarditis.

Q. Explain briefly about Raynaud's phenomenon.

Q. Discuss the clinical presentation and management of Raynaud's disease.

Aetiology of Raynaud's Phenomenon

- Idiopathic (Raynaud's disease)	- Cryoglobulinaemia
- β-blockers and ergot	- Systemic sclerosis
- Pneumatic drill usage	- CRST syndrome
- Occupational exposure to cold	- SLE, rheumatoid arthritis, Sjogren's syndrome
- Peripheral vascular disease	- Diabetes mellitus

Clinical Features

- More common in females.
- Raynaud's phenomenon—On exposure to cold, fingers and less commonly toes become initially very pale (due to vasospasm of digital arteries and concomitant reduction in blood flow), then cyanosed (due to pooling of deoxygenated blood) and then red and painful (due to refilling of vasospastic vessels with oxygenated blood). Approximately 60% of patients will exhibit all three colour changes. Some patients will exhibit only one or two of these changes. These changes are associated with throbbing pain.
- Raynaud's phenomenon can also result from emotional stress.

- As the digital arteries become more constricted, other outward changes including chronic paronychia, nail pitting, hair loss, scarring, fissures and ulcerations of fingers become apparent.
- It can eventually lead to tissue necrosis and gangrene.
- Patients have been documented to have decreases in myocardial perfusion during cold challenge, and there is a higher incidence of angina in patients with Raynaud's phenomenon.
- It should not be confused with acrocyanosis—a disorder primarily affecting young women in which digits turn blue whenever exposed to cold but there is no pain or any of the other outward physical changes associated with Raynaud's phenomenon.

Nail Capillary Microscopy

- Enlarged or distorted capillary loops and a relative paucity of loops suggest an underlying connective tissue disease including systemic sclerosis.

Raynaud's Disease

- Also known as idiopathic Raynaud's phenomenon.
- Age of onset between 15 and 30 years of age.
- More common in females.
- Symmetric episodic attacks without any evidence of peripheral vascular disease, tissue gangrene, digital pitting, negative nail fold capillary examination, normal ESR and negative antinuclear antibody test.

Treatment

- Stop smoking and withdraw offending drugs
- Avoid exposure to cold
- Treatment of underlying cause
- Nifedipine 10 mg thrice daily. If patient is unable to tolerate it, amlodipine may be tried
- Analgesics
- If calcium channel blockers fail, other options are prostaglandins (e.g. iloprost), phosphodiesterase-5 inhibitors (sildenafil, tadalafil, and vardenafil), endothelin receptor antagonists (e.g. bosentan).
- Amputation is rarely needed

Q. Classify aortic aneurysms. What are the common causes of aortic aneurysms?

- Types of aortic aneurysms:
  - Fusiform aneurysm
  - Saccular aneurysm
- Sites of aortic aneurysms:
  - Thoracic part of aorta
    - Ascending aorta
    - Arch of aorta
    - Descending aorta
  - Abdominal aorta
    - Any part of abdominal aorta, but commonest site being infrarenal portion
- Aetiology of aortic aneurysms:
  - Atherosclerosis (commonest cause)
  - Cystic medial necrosis
  - Syphilis (aneurysm of ascending aorta)
  - Rheumatic aortitis
  - Trauma

Q. Discuss the clinical manifestations, complications, investigations and management of abdominal aortic aneurysms (AAA).

- An aneurysm is a permanent focal, full-thickness dilatation of an artery to 1.5 times its normal diameter. Normal infrarenal aortic diameters in patients >50 years are 1.5 cm in females and 1.7 cm in males. By convention, an infrarenal aorta 3 cm in diameter or larger is considered aneurysmal.

- The most common cause of abdominal aortic aneurysm is atherosclerosis. Smoking is an important risk factor for AAA.
- Common in males over 60 years.
- Most common location is between the renal arteries and the iliac arteries.
- Clinical features of abdominal aortic aneurysms:
  - Most cases are asymptomatic.
  - Typically, aneurysms are noted on studies performed for other reasons, as opposed to during physical examination.
  - Symptoms are back pain, abdominal pain and claudication.
  - Physical sign is a pulsatile, non-tender mass in the abdomen. It imparts an expansile pulsation.
  - Classic presentation of a ruptured aneurysm includes the triad of hypotension, abdominal, flank or back pain, and a pulsatile abdominal mass. However, pulsatile mass is often absent after rupture. Other common symptoms include urinary retention, constipation, urge to defaecate, and haematuria.
- Complications of abdominal aortic aneurysms:
  - "Leaking aneurysm" is characterised by severe abdominal pain and tenderness.
  - "Ruptured aneurysm" is characterised by acute severe abdominal pain and hypotension.
- Investigations in abdominal aortic aneurysms:
  - Abdominal radiograph might show the calcified outline of the aneurysm.
  - Ultrasonography (unreliable after rupture but should be performed while resuscitating patient).
  - CT scan (gold standard for diagnosing rupture if patient is haemodynamically stable) and MRI.
  - Angiography confirms the diagnosis.
- Management of abdominal aortic aneurysms:
  - Rupture—Emergency surgery
  - Asymptomatic
    - Aneurysms of more than 5.5 cm diameter—Surgery
    - Aneurysms of less than 5.5 cm diameter—Serial follow-up with ultrasound
  - Surgical treatment of abdominal aortic aneurysm is excision and replacement with a graft
  - Another new option is endovascular repair using an expandable graft system

Q. Discuss the clinical features, investigations and management of aneurysm of thoracic aorta.

Q. How do you classify aneurysms of thoracic aorta?

Classification

- Aneurysm of ascending aorta
- Aneurysm of arch of aorta
- Aneurysm of descending thoracic aorta

Clinical Features

- Clinical features of aneurysms of thoracic aorta may be discussed under four major headings.

General Features

- These are features common to aneurysms of ascending, arch and descending thoracic aorta.
- Pain due to compression or erosion of adjacent musculoskeletal structures.
- Visible and pulsatile (expansile) mass over anterior chest in the corresponding area.
- Rupture is characterised by excruciating pain (may rupture into bronchus, pleura, oesophagus, mediastinum, pulmonary artery or pericardium).

Clinical Features of Aneurysm of Ascending Aorta

- Commonest cause of aneurysm of ascending aorta is cystic medial necrosis—Syphilis was the most common cause a few decades ago.
- Pulsations in the second and third right intercostal spaces.
- Right parasternal dullness on percussion.
- Aortic regurgitation from aortic valve ring dilatation.
- Aortic ejection systolic murmur and a "tambour" like A_2.
- Superior vena caval syndrome from pressure on superior vena cava.
- Dry cough and recurrent pneumonias from compression of right main bronchus.
- Compression of pulmonary artery.

Clinical Features of Aneurysm of Arch of Aorta

- Suprasternal pulsations and pulsations over manubrium sterni
- Dullness on percussion over the upper part of sternum
- Right and left radial pulse difference
- Tracheal tug is a tugging sensation felt when the neck is extended and larynx is held up
- Cough, dyspnoea, stridor and recurrent pneumonias from tracheobronchial compression
- Dysphagia from oesophageal compression
- Hoarseness of voice from recurrent laryngeal nerve compression
- Horner's syndrome from sympathetic nerve compression
- Hiccups and diaphragmatic paralysis from phrenic nerve compression
- Vertebral pain from vertebral compression

Clinical Features of Aneurysm of Descending Thoracic Aorta

- Compression of lung
- Erosion of vertebrae and ribs
- Erosion of nerve roots

Investigations

- Commonly done investigations include chest radiography, electro-cardiogram, ultrasonogram, CT scan, MRI and angiogram.

Treatment

- Only definitive treatment is surgical

Q. Discuss the predisposing factors, classification, clinical features, investigations and management of aortic dissection.

- Aortic dissection is caused by a tear of the intima. The dissection usually propagates distally, but may also propagate proximally. The dissection usually results in aortic dilatation, resulting in dissecting aneurysm of aorta.
- Afflicts males more than females in their fifth and sixth decades.

Predisposing Factors

- Systemic hypertension (70%)
- Cystic medial necrosis, Marfan's syndrome
- Bicuspid aortic valve (BAV)
- Coarctation of aorta (COA)
- Third trimester of pregnancy
- Giant cell arteritis
- Behcet's disease
- Syphilis
- Trauma

Classification

Stanford classification	DeBakey classification
- Type A—dissection involving the ascending aorta independent of site of tear and distal extension - Type B—dissection limited to descending aorta	- Type I—involves ascending to descending aorta - Type II—limited to ascending or arch of aorta - Type III—involves descending aorta only

Clinical Features

- Sudden onset pain in the front or back of chest, often in the interscapular area. The pain is described as "severe and tearing".
- Syncope, dyspnoea and weakness.
- Hypertension or hypotension.
- Asymmetry of pulses and blood pressure in upper limbs (in 30% cases only).
- Dissection can occlude orifices of branches of aorta resulting in ischaemia of brain, heart, bowel, kidney, spinal cord (paraplegia), and extremities (leg pain and paraesthesias).

- Pulmonary oedema.
- In the event of development of a "dissecting aneurysm", symptoms resulting from compression of superior vena cava, superior cervical ganglion, bronchus and oesophagus can manifest.
- Aortic regurgitation, haemopericardium and cardiac tamponade can occur in type A dissection with retrograde propagation.
- Bicuspid aortic valve is commonly associated with dissection and can produce a systolic murmur.

Investigations

- Chest radiography.
  - Dissection involving ascending aorta presents as widening of superior mediastinum and a small pleural effusion, usually left sided.
  - Dissection involving descending thoracic aorta presents as widening of mediastinum. Descending aorta may appear wider than ascending aorta.
- Electrocardiogram to differentiate from acute myocardial infarction. It shows non-specific ST-T wave changes.
- Aortography confirms the diagnosis but is rarely done presently.
- Echocardiography—limited value for evaluation of the entire thoracic aorta for dissection but is highly useful in identifying proximal aortic dissection.
- Spiral CT scan is the modality of choice for diagnosis.
- Magnetic resonance imaging is useful in some patients.

Treatment

- Type A dissection is preferably treated by emergency surgical correction.
- Type B dissection that is stable and uncomplicated is preferably treated by medical measures (in selected cases, surgical treatment is indicated).
  - Medical therapy is aimed at reducing cardiac contractility and systemic arterial pressure to 100–120 mmHg systolic.
    - Parenteral administration of a β-blocker (esmolol or metoprolol) with sodium nitroprusside infusion. Target is to achieve a systolic blood pressure of 100–120 mmHg and a pulse of 60–80/minute.
    - If β-blockers are contraindicated, parenteral calcium channel blockers may be used.
    - If β-blockers alone do not control blood pressure, vasodilators (e.g. sodium nitroprusside or nitroglycerine) may be given.
    - Direct vasodilator (diazoxide and hydralazine) as monotherapy are contraindicated because they increase the force of left ventricular ejection.
  - Surgical therapy involves reconstruction of the aorta. Another option for type B dissection is endovascular technique.

Q. Discuss the clinical spectrum of cardiovascular syphilis.

- Manifestations of cardiovascular syphilis are seen in the tertiary stage. They include the following:
  - Aortitis
  - Aortic regurgitation
  - Aneurysm of aorta
  - Coronary ostial stenosis
  - Myocardial gumma
  - Endarteritis
- Aortitis—Commonly involves ascending aorta. Clinical features include burning retrosternal chest pain, dilatation of aorta, aortic ejection systolic murmur and a loud "tambour" like second heart sound.
- Aortic regurgitation—For a detailed account of syphilitic aortic regurgitation, refer aortic regurgitation.
- Aneurysms of aorta—Clinical manifestation of syphilitic aortic aneurysms are discussed under aortic aneurysm.
- Coronary ostial stenosis—Manifests as angina (nocturnal angina), sudden death or arrhythmias. Myocardial infarction is rare.
- Myocardial gumma—Clinical diagnosis is extremely difficult. Might manifest as bundle branch block, AV block or rarely ECG pattern simulating myocardial infarction.
- Diagnosis of cardiovascular syphilis is based on syphilitic serological tests (positive TPHA and VDRL).
- Treatment of cardiovascular syphilis is with parenteral penicillin for 2 weeks.

Q. Mention the common causes of left ventricular hypertrophy.

• Systemic hypertension	• Coarctation of aorta (COA)
• Aortic stenosis (AS)	• Hypertrophic cardiomyopathy (HCM)

Q. Mention the common causes of left ventricular dilatation.

- Aortic regurgitation (AR)
- Mitral regurgitation (MR)
- Ventricular septal defect (VSD)
- Persistent ductus arteriosus (PDA)

- Dilated cardiomyopathy
- Ischaemic heart disease (IHD)
- Hyperkinetic circulatory states like anaemia, thyrotoxicosis and beriberi

Q. Discuss the differential diagnosis of ejection systolic murmurs (ESM).

Q. Discuss in brief about straight back syndrome (SBS).

Q. Give a brief outline of idiopathic dilatation of pulmonary artery (IDPA).

Q. Write a short note on sclerotic aortic valve disease.

Q. Discuss briefly about bicuspid aortic valve (BAV).

- Ejection systolic murmur (ESM), also known as midsystolic murmur starts shortly after the first heart sound (S_1) and ends before the second heart sound. It is a crescendo–decrescendo or diamond-shaped murmur.
- ESMs are usually produced at aortic or pulmonary valves.

Ejection systolic murmur (ESM)
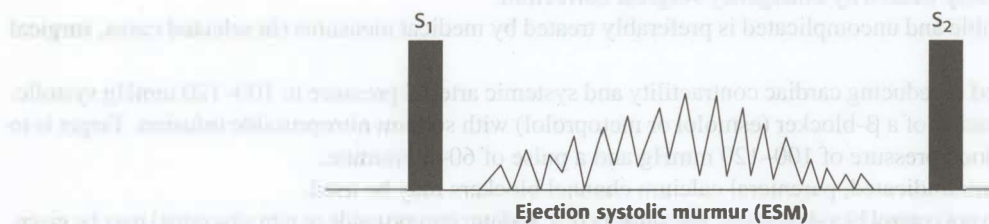
Causes

Organic valvular diseases
- Aortic stenosis (AS)
- Pulmonary stenosis (PS)
- Hypertrophic cardiomyopathy (HCM)
- Sclerotic aortic valve
- Bicuspid aortic valve (BAV)
- Tetralogy of Fallot (TOF)

Flow murmur from extracardiac causes
- Exercise, pregnancy
- Thyrotoxicosis
- Severe anaemia
- Systemic arteriovenous fistulae

Flow murmur from intracardiac causes
- Atrial septal defect (ASD)
- Aortic regurgitation (AR)
- Mitral regurgitation (MR)

Miscellaneous
- Coarctation of aorta (COA)
- Thin chest wall
- Pectus excavatum
- Straight back syndrome (SBS)
- Idiopathic dilatation of pulmonary artery
- Aneurysm of ascending aorta
- Innocent murmur

Note: 1. Flow ejection murmurs occur due to increased flow across semilunar (aortic or pulmonary) valves
2. Mitral valve prolapse produces late systolic murmur

Differential Diagnosis

- Diagnosis is based on the behaviour of the murmur and associated features.

Aortic Stenosis (AS)

Murmur

- Loud harsh ejection systolic murmur best heard in the second right intercostal space (aortic area), radiating to carotid arteries. It diminishes with sustained hand grip.

Associated Features

- Pulsus tardus and low systolic blood pressure (less than 100 mmHg).
- Left ventricular hypertrophy and heaving apical impulse.
- Systolic thrill at the second right intercostal space, radiating to lower left sternal border and carotids ("cross-belt" area).
- Intensity of A_2 is decreased or A_2 may even be absent.
- Second heart sound may be single or narrowly split or rarely paradoxically split.
- Aortic ejection sound in second right intercostal space in valvular aortic stenosis.

Pulmonary Stenosis (PS)

Murmur

- Loud harsh ejection systolic murmur best heard at the second left intercostal space (pulmonary area), radiating towards left shoulder. The murmur increases with inspiration and decreases with expiration.

Associated Features

- Prominent a waves on JVP.
- Left parasternal heave and epigastric pulsations due to right ventricular hypertrophy.
- Systolic thrill at the second left intercostal space (pulmonary area).
- Wide splitting of second heart sound due to delay in right ventricular ejection and hence delayed P_2.
- Pulmonary component (P_2) of second heart sound is soft or may even be absent.
- Murmur is often preceded by a pulmonary ejection sound.

Hypertrophic Cardiomyopathy (HCM)

Murmur

- Harsh ejection systolic murmur best heard at the lower left sternal border as well as at the apex with no radiation. The murmur increases during standing and Valsalva manoeuvre. It decreases during squatting and sustained handgrip.

Associated Features

- Rapidly rising ("jerky") carotid pulse
- Double apical impulse (bifid apical impulse)
- Giant presystolic parasternal heave
- Loud fourth heart sound
- Pansystolic murmur at the apex due to associated mitral regurgitation (MR)

Sclerotic Aortic Valve

- About 50% of the people over the age of 50 years have an aortic ejection systolic murmur from a sclerotic aortic valve without valve stenosis. It is benign, non-stenotic (non-obstructive) deformity of the aortic valve of old age.

Murmur

- Rough ejection systolic murmur of short duration (but less harsh and less intense than aortic stenosis murmur), best heard in the second right intercostal space (aortic area), commonly radiating to apex and may even be maximal at the apex.

Associated Features

- Thrill is rare.
- Arterial pulse, JVP, apical impulse and heart sounds are normal.
- No extra sounds are audible.
- No other murmurs of other valvular lesions are audible.

Bicuspid Aortic Valve (BAV)

- Common cause of isolated aortic stenosis.
- Increased risk of infective endocarditis.

Murmur

- Soft ejection systolic murmur in the second right intercostal space (aortic area).

Associated Features

- Arterial pulse, JVP, apical impulse and heart sounds are normal.
- The murmur is usually preceded by an aortic ejection sound.

- Associated aortic regurgitation may be present.
- Associated aortic stenosis, coarctation of aorta or dissection of aorta may be present.

Tetralogy of Fallot (TOF)

Murmur

- Loud, harsh ejection systolic murmur best heard at the second and third left intercostal spaces due to pulmonary stenosis.

Associated Features

- Cyanotic spells ("Fallot spells")
- Squatting
- Central cyanosis, finger clubbing and polycythaemia
- Prominent *a* waves on JVP if pulmonary stenosis is severe
- Systolic thrill may be felt in the second or third left intercostal spaces
- Second heart sound is single due to absent pulmonary component (P_2)

Atrial Septal Defect (ASD)

Murmur

- Ejection systolic murmur at the second left intercostal space (pulmonary area) due to increased flow of blood across the pulmonary valve.

Associated Features

- Hyperdynamic precordium
- Pulsations in the second left intercostal space from dilated pulmonary artery
- Systolic thrill over second left intercostal space (pulmonary area)
- Wide and fixed splitting of second heart sound in relation to respiration
- Rumbling mid diastolic flow murmur at tricuspid area

Coarctation of Aorta (COA)

Murmur

- Ejection systolic murmur over the spine posteriorly from the coarctation itself.

Associated Features

- Underdeveloped lower segment of the body
- Hypertension in the upper limbs
- Radiofemoral delay
- "Suzman's sign"—pulsatile collaterals around scapulae and intercostal regions in the back
- "Cork-screw" shaped retinal arteries
- Heaving apical impulse
- Aortic ejection sound in associated bicuspid aortic valve
- Systolic or continuous murmurs over lateral thoracic wall arising from collaterals
- Ejection systolic murmur and/or early diastolic murmur over the second right intercostal space (aortic area) from the associated bicuspid aortic valve

Thin Chest Wall

- Increased transmission of sound through the thin chest wall can cause an ejection systolic murmur over precordium in otherwise normal people.

Pectus Excavatum

- The murmur is the result of distortion of the underlying structures by the deformity
- Soft ejection systolic murmur, best heard at the base of the heart
- No evidence of chamber enlargement or abnormal heart sounds

Straight Back Syndrome (SBS)

- In SBS, the normal thoracic kyphosis of the spine is lost and thoracic spine becomes "straight". This results in a reduction of anteroposterior diameter of the thorax, and the heart is compressed between the sternum anteriorly and the spine posteriorly. The murmur results from the distortion of the outflow tract and great vessels.

- Ejection systolic murmur is best heard at the second left intercostal space (pulmonary area). It is probably caused by compression of right ventricular outflow tract by sternum which reduces with deep inspiration.
- Examination of the spine reveals absence of the normal thoracic kyphosis.
- No evidence of chamber enlargement or abnormal heart sounds.
- ECG often shows right bundle branch block.

Idiopathic Dilatation of Pulmonary Artery (IDPA)

- Dilatation of main pulmonary artery, with or without dilatation of right and left pulmonary arteries.
- Ejection systolic murmur best heard at the second left intercostal space (pulmonary area). The murmur increases during inspiration.
- Pulsations in the second left intercostal space from the underlying dilated pulmonary artery.
- No signs of right ventricular hypertrophy.
- Ejection sound at the pulmonary area.
- Pulmonary component (P_2) of the second heart sound may be loud.
- No cardiac or extracardiac shunts.
- No chronic pulmonary disease.

Q. Discuss the differential diagnosis of pansystolic (holosystolic) murmurs (PSM) over precordium.

- Pansystolic murmur (PSM) starts immediately with the first heart sound and continues through to the second heart sound. Typically, it has a uniform intensity throughout.

Pansystolic murmur (PSM)

Causes

- Mitral regurgitation (MR)	- Ventricular septal defect (VSD)
- Tricuspid regurgitation (TR)	- Aortopulmonary shunts (rare)

Differential Diagnosis

- Diagnosis is based on the behaviour of the murmur and associated features.

Mitral Regurgitation (MR)

Murmur

- High-pitched, blowing, pansystolic murmur best heard at the apex. It commonly radiates to axilla and back (left inter-scapular area) when the anterior mitral leaflet is predominantly involved. With predominant posterior mitral leaflet involvement the murmur radiates to left sternal border and base of heart.
- It increases during expiration, sustained handgrip and transient exercise. The murmur is unchanged or decreases during inspiration.

Associated Features

- High volume collapsing pulse and wide pulse pressure.
- "Rocking motion" of the precordium.
- Apical impulse is hyperdynamic in character and shifted down and out.
- Systolic thrill at the apex.
- First heart sound is soft.
- Second heart sound is widely split, but mobile.
- Left ventricular third heart sound is common.
- Rumbling, mid diastolic flow murmur at the apex in pure severe mitral regurgitation.

Tricuspid Regurgitation (TR)

Murmur

- Blowing pansystolic murmur best heard at the lower-left sternal border (tricuspid area), radiating to lower right sternal border or pulmonary area. It may be heard up to the apex, but never beyond it. The murmur is intensified during inspiration and decreases during expiration (De-Carvallo's sign).

Associated Features

- JVP shows prominent v waves and rapid y descent
- Hepatomegaly with systolic pulsations
- Signs of pulmonary hypertension including functional tricuspid regurgitation
- Rarely systolic thrill at lower left sternal border
- Right ventricular third heart sound may be heard
- Rumbling mid diastolic flow murmur at lower-left sternal border in pure severe tricuspid regurgitation (TR).

Ventricular Septal Defect (VSD)

Murmur

- Harsh pansystolic murmur best heard at the third or fourth left intercostal space, but radiating all over precordium. The murmur increases during transient exercise, but is unchanged by respiration.

Associated Features

- High volume collapsing pulse
- Hyperdynamic precordium
- Apical impulse is hyperdynamic in character and shifted down and out
- Systolic thrill at the third or fourth left intercostal space
- Second heart sound is widely split, but mobile
- Left ventricular third heart sound is common
- Rumbling mid diastolic flow murmur at the apex in large shunts.

Q. Discuss the differential diagnosis of mid-diastolic murmurs (MDM).

Q. Briefly outline left atrial myxoma, Carey–Coombs murmur and Austin Flint murmur.

- Mid-diastolic murmur (MDM) is characterised by a short gap after the second heart sound, before the beginning of the murmur.
- MDM usually arises from the atrioventricular valves (mitral valve and tricuspid valve). They result from a disproportion between valve orifice size and flow rate. The classical MDM of mitral stenosis is shown below:
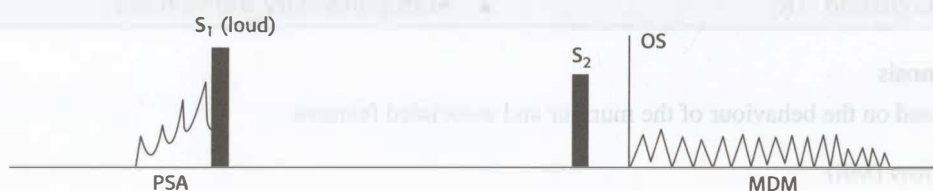
Causes

At the apex	At the tricuspid area

- **Organic**
    - Mitral stenosis (MS)
    - Rheumatic carditis (Carey–Coombs murmur)
    - Left atrial myxoma
    - Left atrial valve thrombus
 	
 - **Functional** (due to increased flow)
    - Aortic regurgitation (Austin Flint murmur)
    - Mitral regurgitation (MR)
    - Ventricular septal defect (VSD)
    - Persistent ductus arteriosus (PDA)
	- **Organic**
	    - Tricuspid stenosis(TS)
	
	 - **Functional** (due to increased flow)
	    - Atrial septal defect (ASD)
	    - Severe tricuspid regurgitation (TR)

Differential Diagnosis

- Diagnosis is based on the behaviour of the murmur and associated features.

Mitral Stenosis (MS)

Murmur

- Mid-diastolic murmur, often with a presystolic accentuation, well localised to the apex. It is low-pitched, rough and rumbling in character, best heard at the apex with the bell of the stethoscope, with the patient in left lateral position and during expiration. Murmur is accentuated by exercise carried out just before auscultation.

Associated Features

- Mitral facies
- Tapping apical impulse with a diastolic thrill
- Evidence of atrial fibrillation
- Evidence of pulmonary hypertension
- Loud first heart sound
- Opening snap (OS)
- Loud pulmonary component (P_2) of second heart sound in pulmonary hypertension.
- Pansystolic murmur of tricuspid regurgitation in advanced cases with right ventricular dilatation.
- Early diastolic murmur of pulmonary regurgitation in advanced pulmonary hypertension.

Carey Coombs Murmur of Rheumatic Carditis

Murmur

- Soft mid diastolic murmur, well localised to the apex

Associated Features

- Fever
- Migratory polyarthritis
- Subcutaneous nodules
- Erythema marginatum
- Chorea
- Evidence of myocarditis like tachycardia, third and fourth heart sounds, summation gallop, "tic-tac" quality of heart sounds, arrhythmias and heart failure.
- Evidence of endocarditis like apical pansystolic murmur of mitral regurgitation and basal early diastolic murmur of aortic regurgitation.
- Evidence of pericarditis like pericardial pain and pericardial friction rub.

Left Atrial Myxoma

- Left atrial myxoma is a pedunculated, polypoidal, benign tumour arising from left atrium. It obstructs the mitral valve, resulting in murmurs of stenosis or regurgitation. Diagnosis is by echocardiography and cardiac MRI. Surgical excision is required because of complications including sudden death.

Murmur

- Mid-diastolic murmur, often with a presystolic accentuation, best heard at the apex. The character and duration of the murmur vary from time to time or with a change in the position of the patient.

Associated Features

- Higher incidence in females.
- Systemic features like fever, fatigue, anaemia and weight loss are very common (in 90%).
- Systemic embolisation of tumour fragments or surface clots is common.
- Pulmonary hypertension and right heart failure can occur.
- First heart sound is loud.
- Pulmonary component (P_2) of the second heart sound is usually loud.
- "Tumour plop" is an early diastolic sound.
- Apical systolic murmur from associated mitral regurgitation (MR).
- Anaemia and increase in ESR, CRP and globulin levels.

- Presence of constitutional symptoms, persistence of sinus rhythm, shorter duration of illness and changing character of murmur with posture and time differentiate left atrial myxoma from rheumatic mitral stenosis

Austin Flint Murmur of Aortic Regurgitation (AR)

Murmur

- Rumbling mid-diastolic murmur, without a presystolic accentuation even in the presence of sinus rhythm. It is best heard at the apex. It is separate from early diastolic murmur of AR

Associated Features

- Peripheral signs of aortic regurgitation
- Hyperdynamic precordium
- Hyperdynamic apical impulse that is shifted down and out
- Left ventricular third heart sound
- Early diastolic murmur of aortic regurgitation in the Erb's area or aortic area
- Aortic ejection systolic murmur due to increased flow

Mitral Regurgitation (MR), Ventricular Septal Defect (VSD) and Persistent Ductus Arteriosus (PDA)

- These conditions are associated with an increased flow of blood across the mitral valve, resulting in a mid diastolic murmur.

Murmur

- Rumbling mid-diastolic murmur, best heard at the apex.

Associated Features

- All these conditions result in a hyperdynamic apex that is shifted down and out, and left ventricular third heart sound.
- Mitral regurgitation (MR).
    - Systolic thrill at apex
    - Soft first heart sound
    - Pansystolic murmur at apex radiating to axilla and back
- Ventricular septal defect
    - Systolic thrill at third or fourth left intercostal space
    - Widely split, but mobile second heart sound
    - Pansystolic murmur maximal at third or fourth left intercostal space and radiating all over precordium
- Persistent ductus arteriosus
    - Continuous thrill at the upper left sternal edge
    - Continuous "machinery murmur" with late systolic accentuation at the upper left sternal edge

Tricuspid Stenosis (TS)

Murmur

- Mid-diastolic murmur, often with a presystolic accentuation, best heard at the lower left sternal border (tricuspid area). The murmur increases during inspiration (De-Carvallo's sign).

Associated Features

- Refractory oedema and ascites
- Hepatomegaly with presystolic pulsations
- Raised jugular venous pressure with prominent *a* waves (giant *a* waves) and slow *x* descent
- Loud first heart sound and tricuspid OS

Atrial Septal Defect (ASD) and Tricuspid Regurgitation (TR)

- These conditions are associated with an increased flow of blood across the tricuspid valve, resulting in MDM.

Murmur

- Rumbling mid-diastolic murmur, best heard at the lower left sternal border (tricuspid area)

Associated Features

- Atrial septal defect
    - Hyperdynamic precordium

- Pulsations in the second left intercostal space
- Wide and fixed splitting of second heart sound
- Ejection systolic murmur at the second left intercostal space (pulmonary area)
- Tricuspid regurgitation
  - Hepatomegaly with systolic pulsations
  - Raised jugular pressure with prominent *v* waves and rapid *y* descent
  - Blowing pansystolic murmur at the lower left sternal border, which is intensified during inspiration

Q. Enumerate the common causes of continuous murmurs.

- Continuous murmurs begin in systole, peak near second heart sound and continue into diastole.
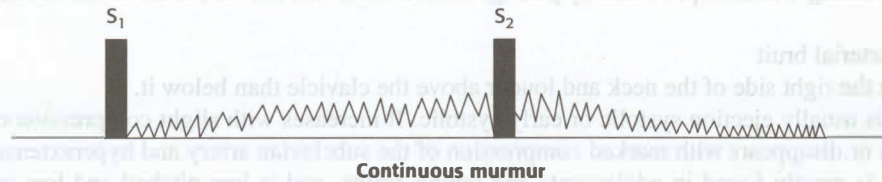
Continuous murmur

Causes

Continuous murmurs
• Persistent ductus arteriosus (upper left sternal edge)
• Surgically produced shunts in tetralogy of Fallot (right or left or upper sternum)
• Systemic arteriovenous fistula (directly over the fistula)
• Coarctation of aorta (posteriorly over the spine and lateral chest wall)
• Pulmonary arteriovenous fistula (over lower lobe or right middle lobe of lung)
• Coronary arteriovenous fistula (apicosternal region)
• Anomalous origin of the left coronary artery from the pulmonary artery
• Rupture of aneurysm of sinus of Valsalva (fourth left intercostal space)
• Jugular venous hum (medial aspect of the right supraclavicular fossa)
• Mammary souffle (right or left sternal border, from second to fourth intercostal spaces)

Q. Write a brief note on innocent murmurs.

Q. Describe briefly about venous hum (jugular venous hum; cervical venous hum).

Q. Explain mammary souffle.

- Innocent murmurs are those not due to recognisable lesions of the heart or blood vessels. They are most common in children and adolescents.

What not is an Innocent Murmur?

• Diastolic murmurs
• Loud murmurs, grade IV or above
• Regurgitant (pansystolic) murmurs
• Murmurs associated with a click
• Murmurs associated with other signs or symptoms (e.g. cyanosis)
• Abnormal second heart sound (fixed split or single)

Types of Innocent Murmurs

- Pulmonary ejection murmur
  - Originates in the right ventricular outflow area to the pulmonary arteries.
  - It is high pitched and is best heard with diaphragm of stethoscope in the second left intercostal space (pulmonary area) with radiation to lower left sternal border and apex.

- The murmur is usually ejection systolic and is heard at the beginning of systole or mid-systole. It is louder on lying down and held expiration. It is heard more clearly in situations of increased cardiac output such as fever, anxiety, acute disease and post-exercise; it decreases with the Valsalva manoeuvre and standing position.
- In contrast to pulmonary valvular stenosis, there is no ejection click or thrill.
- Most common in children and adolescents aged between 8 and 14, particularly those with pectus excavatum or kyphoscoliosis.
- Vibratory murmur or Still's murmur
  - Found in many school age children.
  - Best heard at the lower left sternal border or apex with wide radiation.
  - The murmur is usually ejection systolic or early systolic with a musical or twanging quality. It increases with the patient lying down and decreases in the erect posture. The murmur might disappear on extension of the neck.
  - It results from changes in flow produced by passage from the left ventricle to the aorta. However, exact pathogenesis is not clear.
- Supraclavicular arterial bruit
  - Best heard on the right side of the neck and louder above the clavicle than below it.
  - The murmur is usually ejection systolic or early systolic. It increases with slight compression of subclavian artery and decreases or disappears with marked compression of the subclavian artery and hyperextension of shoulder.
  - This murmur is mostly found in adolescents and young adults, and is low-pitched and low intensity, sometimes associated with slight neck thrill.
- Venous hum (jugular venous hum; cervical venous hum).
  - Best heard at the root of the neck over the medial part of supraclavicular fossa (just lateral to sternocleidomastoid) with the head turned in the opposite direction. It is more common on the right side.
  - The murmur is continuous murmur that increases on sitting up. It decreases on lying down and is obliterated by compression of internal jugular vein, and by turning neck towards the side of murmur.
  - It originates where jugular, subclavian and brachiocephalic veins join the superior vena cava.
  - Mainly detected in children aged between 3 and 8.
- Mammary souffle
  - Best heard at the right or left sternal border, extending from second to fourth intercostal spaces.
  - The murmur is a continuous murmur with systolic accentuation. It occurs in late pregnancy and during lactation. The murmur is obliterated by firm pressure with the stethoscope. It disappears after lactation.

Q. How do you differentiate bronchial asthma from cardiac asthma?

Bronchial asthma	Cardiac asthma
• Longer duration of breathlessness	• Shorter duration of breathlessness
• Usually occurs in early morning hours	• Usually occurs 2–3 hours after sleep
• Scanty whitish sputum	• Copious pink frothy sputum
• No cardiomegaly	• Cardiomegaly may be present
• No third heart sound	• Third heart sound is heard
• Evidence of pulmonary disease	• Evidence of cardiac disease
• Predominantly rhonchi	• Starts with fine basal crepitations
• Usually relieved by bronchodilators	• Usually relieved by sitting up or diuretics
• Chest X-ray shows hyperinflation and normal heart size	• Chest X-ray shows cardiomegaly and other evidence of pulmonary oedema
• Electrocardiogram is usually normal	• Electrocardiogram is usually abnormal

Chapter 8

Diseases of the Gastrointestinal System

Q. What are the common causes of loss of appetite (anorexia)?

- Infections—viral fever and pulmonary tuberculosis.
- Endocrine causes—hypothyroidism, Addison's disease, hyperparathyroidism and panhypopituitarism
- Liver diseases—hepatitis and cirrhosis
- Renal disease—chronic renal failure
- Malignancies—carcinoma stomach, pancreas or any other malignancy
- Leukaemias and lymphomas
- Psychiatric—depression and anorexia nervosa

Q. What are the common causes of persistent vomiting?

- Acute abdominal emergencies or surgical abdomen—acute appendicitis, acute pancreatitis, acute cholecystitis, intestinal obstruction and acute peritonitis
- Gastroesophageal reflux and gastroparesis
- Acute systemic infections with fever—hepatitis, viral, bacterial and parasitic infestations of intestine
- Central nervous system disorders—raised intracranial tension, cerebral tumours, meningitis and encephalitis
- Disorders of labyrinth or its connections—acute migraine, acute labyrinthitis and Meniere's disease
- Endocrine disorders—diabetic ketoacidosis, adrenal crisis and morning sickness of early pregnancy
- Congestive cardiac failure and acute myocardial infarction
- Psychogenic vomiting

Q. What are the causes of hiccough in an elderly male? Give the symptomatic treatment of hiccough.

- Hiccough is a phenomenon resulting from sudden spasmodic involuntary contraction of the diaphragm with the glottis remaining closed.
- Causes
  - Hasty ingestion of food and fluids
  - Irritation of the phrenic nerve from compression by tumours, pericarditis, mediastinitis, surgery of thorax and abdomen
  - Cerebrovascular accidents, encephalitis, brain tumours, renal failure, hepatic failure, diabetic ketoacidosis, respiratory failure and electrolyte imbalance
  - Local irritation of the diaphragm from gaseous distension of stomach and intestines, subphrenic abscess, peritonitis and acute myocardial infarction
  - Psychogenic
  - Obscure

Symptomatic Treatment

- Drinking cold water
- Pressure over the eyeballs
- Valsalva manoeuvre
- Pull on the tongue
- Rebreathing into a paper bag
- Local infiltration of phrenic nerve with procaine
- Drug therapy:
  - Chlorpromazine 25–50 mg orally or intramuscularly
  - Domperidone 10 mg thrice daily

- Metoclopramide 10 mg thrice daily
- Xylocaine viscus 15 mL thrice a day

Q. Define constipation. What are the common causes of constipation? Discuss briefly about its management.

- Constipation—patients having bowel movements less frequently than three times a week. If stool is hard and difficult to pass, patient is constipated whatever be the frequency.

Rome III Criteria for Defining Constipation

- Two or more of the following for at least 12 weeks with onset ≥6 months:
  - Straining during ≥25% of defecations
  - Lumpy or hard stools in at least 25% of defecations
  - Sensation of incomplete evacuation for at least 25% of defecations
  - Sensation of anorectal obstruction or blockade for at least 25% of defecations
  - Digital evacuation to facilitate ≥25% of defecations
  - Fewer than three defecations per week
- Loose stools are rarely present without the use of laxatives
- Insufficient criteria for irritable bowel syndrome

Causes

Acute
- Dehydration
- Acute intestinal obstruction
- Acute appendicitis

Chronic
I. Functional
   A. Rectal stasis
      - Faulty habits
      - Impaired consciousness
      - Painful anal area (anal fissure)
   B. Colonic stasis
      - Decreased food intake
      - Decreased fibre residue
      - Endocrine dysfunction
   C. Irritable bowel syndrome
II. Organic
   A. Endocrine and metabolic diseases
      - Myxoedema
      - Diabetes mellitus
      - Hypercalcaemia
      - Hyperparathyroidism

B. Myopathic diseases
   - Amyloidosis
   - Systemic sclerosis
   - Myotonic dystrophy
C. Neurologic diseases
   - Autonomic neuropathy
   - Cerebrovascular disease
   - Hirschsprung's disease
   - Multiple sclerosis
   - Parkinson's disease
   - Spinal cord diseases
D. Structural diseases
   - Anal fissure
   - Haemorrhoids
   - Megacolon
   - Diverticulitis
E. Psychological conditions
   - Depression
F. Medications (antacids, anticholinergics, antidepressants, antihistamines, calcium, calcium channel blockers, clonidine, diuretics, iron, opioids)
G. Others
   - Pressure on rectum from tumours or gravid uterus

Investigations

- Complete blood count, serum glucose, thyroid stimulating hormone, calcium and creatinine levels
- Stool examination including occult blood
- Sigmoidoscopy or colonoscopy to exclude colon cancer in:
  - Patients older than 50 years
  - Patients with concomitant rectal bleeding or weight loss
  - Patients with haeme-positive stools or iron deficiency anaemia
- Others—colonic transit time, anorectal manometry and balloon expulsion test

Treatment

- Eliminate offending medication
- Treat underlying medical condition causing constipation
- If no secondary cause of constipation identified, empiric treatment for functional constipation
  - Non-pharmacologic methods to improve bowel regularity
  - Laxatives

Non-Pharmacologic Treatment

- Maintain a diary for stool frequency, consistency, size and degree of straining. Many patients incorrectly believe that they need to have a bowel movement every day.
- Patients should be educated on recognising and responding to the urge to defecate.
- Patients should be encouraged to attempt defecation first thing in the morning, when the bowel is more active and 30 minutes after meals to take advantage of the gastrocolic reflex.
- Patients should be encouraged to increase their intake of fibre-rich foods such as bran, fruits, vegetables and nuts.
- Adequate hydration
- Patients should be encouraged to be as physically active as possible

Laxatives

- Bulk laxatives
  - Contain soluble (ispaghula or psyllium, pectin or guar) or insoluble (methyl cellulose) products
  - Absorb water from intestinal lumen to increase stool mass and soften stool consistency
  - Generally well tolerated
  - Bloating and excessive gas production may be the adverse effects
- Emollient laxatives (stool softeners)
  - Include docusate sodium and docusate calcium
  - Act by lowering surface tension, allowing water to enter the bowel more readily
  - Generally well tolerated
  - Useful for patients with anal fissures or haemorrhoids that cause painful defecation
- Mineral oil is not recommended because of potential to deplete fat-soluble vitamins and the risk of aspiration
- Osmotic laxatives
  - Hyperosmolar agents that cause secretion of water into the intestinal lumen by osmotic activity
  - They include:
    - Magnesium hydroxide (milk of magnesia), magnesium citrate and sodium biphosphate, which are relatively safe, but may precipitate hypokalaemia, fluid and salt overload and diarrhoea. These are avoided in patients with congestive heart failure and chronic renal failure.
    - Sorbitol and lactulose that are metabolised by bacteria into hydrogen and organic acids. Poor absorption of these agents may lead to flatulence and abdominal distention.
    - Polyethylene glycol is safe and effective laxative.
- Stimulant laxatives
  - Include senna, castor oil, sodium picosulphate and bisacodyl (also available as suppository)
  - Increase intestinal motility and secretion of water into the bowel
  - Continuous daily ingestion may produce hypokalaemia and protein-losing enteropathy
- Prokinetic agents enhance GI motility by increasing frequency of contractions in small intestine or making them stronger but without disrupting their rhythm.
  - Mosapride, itopride, levosulpiride and prucalopride
- Others
  - Linaclotide is a minimally absorbed peptide agonist of the guanylate cyclase-C receptor that stimulates intestinal fluid secretion and transit. It reduces activation of colonic sensory neurons thereby reducing pain, activates colonic motor neurons, increasing smooth muscle contraction and promoting bowel movements
  - Lubiprostone activates chloride channels on the intestinal epithelial cells, thus secreting chloride and water into gut lumen. May be used in constipation-predominant irritable bowel syndrome

Q. Enumerate the common causes of diarrhoea in the tropics.

Toxin-induced gastroenteritis	Gastroenteritis due to changes in mucosa

• Preformed toxins
  • *Staphylococcus aureus*
  • *Bacillus cereus*
• Enterotoxins produced in the intestine
  • *Vibrio cholerae*
  • *E. coli* (enterotoxigenic)
  • *Clostridium perfringens*
  • *Clostridium difficile*
	• Mucosal alteration without invasion
	  • *Rotavirus*
	  • *Norwalk* agent
	• Invasion of mucosa with destruction
	  • *Shigella*
	  • *E. coli* (enteroinvasive)
	  • *Campylobacter*
	  • *Yersinia enterocolitica*
	  • *Salmonella*
	  • *Entamoeba histolytica*
	• Other causes
	  • Heavy metals (arsenic)
	  • Monosodium glutamate
	  • Mushrooms

Q. Enumerate the intestinal causes of chronic diarrhoea.

1. Chronic enteric infections
   - *Salmonella*
   - *Streptococcus*
   - Fungi
   - Viruses
2. Parasitic causes
   - Amoebic colitis
   - Giardiasis
   - *Leishmania donovani*
   - *Strongyloides stercoralis*
   - Trichuriasis
   - *Cryptosporidium*
   - *Microsporidium* (common in patients with AIDS)
   - *Isospora*

3. Malabsorption syndrome
4. Post-operative—enterocolostomy
5. Intestinal, biliary and gastric fistulae
6. Pellagra
7. Inflammatory bowel diseases
   - Ulcerative colitis
   - Crohn's disease
8. Intestinal tuberculosis
9. Diverticulitis, neoplasms
10. Colitis due to drugs—mercury, arsenic
11. Laxative abuse
12. Miscellaneous—hyperthyroidism, radiation injury, carcinoid, vipoma

Q. What is food poisoning?

- A foodborne disease outbreak, where a cluster of two or more individuals develop similar symptoms following the ingestion of a common food.
- The most common form of food poisoning is gastroenteritis following consumption of food containing preformed toxin or organisms that produce toxin in the gut.
- Common causes have been listed above under "common causes of diarrhoea in the tropics".
- In case of ingestion of contaminated food having preformed toxin, the symptoms of acute upper gastrointestinal upset (nausea and vomiting) start within 6 hours of ingestion. If the food contains organisms that produce toxin in the gut, the main feature is diarrhoea that usually develops within 6–72 hours of exposure.
- Botulism is also a type of food poisoning that does not produce symptoms of gastroenteritis.

Q. How will you evaluate and manage a patient with acute diarrhoea?

- Acute diarrhoea is defined as stool with increased water content, volume (at least 200 g/day), or frequency (at least thrice per day) that lasts <2 weeks.

Evaluation of a Patient with Acute Diarrhoea

- Assess for:
  - Severity of dehydration
  - Requirement for any diagnostic tests
  - Any evident specific cause
  - Requirement for any treatment

History

• Duration of diarrhoea	• Urine output
• Stool volume	• Any change in the level of consciousness
• Frequency of loose stools	• Any other family member or close associate affected
• Appearance of stools (e.g. rice water)	• History of having food outside in the recent past
• Associated blood or mucus in the stools	• Whether the patient is taking any antibiotics
• Associated pain abdomen, fever	• Occupation of the patient
• Associated with vomiting	

Examination

- Assess pulse, blood pressure (including postural change), skin turgor, dryness of mucous membranes, mental status and any acidotic breathing.
- Assess muscle strength and muscle reflexes as these may be reduced in hypokalaemia.
- Examine abdomen to exclude any surgical cause including intestinal obstruction.

Laboratory Investigations

- Laboratory studies in general, are usually not helpful in the acute management of a patient with diarrhoea as most cases are self-limiting.
- Specific diagnostic investigation may be required for patients with severe dehydration, persistent fever, bloody stool, or immunosuppression, and for cases of suspected nosocomial infection or outbreak.
- A high leucocyte count with shift to the left suggests an invasive bacterial infection but may not always be present.
- Lactoferrin—a marker for leucocytes which is released by damaged cells and increases in the setting of bacterial infections.
- In patients with severe dehydration, check electrolytes and acid-base status. Severe diarrhoea produces metabolic acidosis.
- Obtain blood cultures when bacteraemia or a systemic infection is suspected.
- In severe cases, examine stool for the presence of leucocytes, red cells and cysts or trophozoites. Also look for the characteristic darting motility of *V. cholerae* organisms.
- Stool culture if patient has grossly bloody stool, severe dehydration, signs of inflammatory disease, symptoms lasting more than 3–7 days or immunosuppression.
- *Clostridium difficile* toxins A and B for patients who develop unexplained diarrhoea after hospitalisation or during or after antibiotics use.

Severity of Dehydration

Features	Mild dehydration	Moderate dehydration	Severe dehydration
• Urine output	Normal	Reduced	Markedly reduced
• Level of consciousness	Normal	Normal	Depressed
• Oral mucosa	Dry	Markedly dry	Parched
• Skin	Normal	Cool	Cool, mottled
• Skin turgor	Normal	Reduced	Markedly reduced
• Eyes	Normal	Sunken	Markedly sunken
• Pulse rate	Normal or mild increase	Tachycardia	Marked tachycardia
• Blood pressure	Normal	Postural drop or reduced	Shock
• Respiration	Normal	Normal	Acidotic
• Mental status	Normal or irritable	Lethargic	Comatose
• Urine specific gravity	<1.020	>1.020	>1.035
• Blood urea	Normal	Normal to raised	High

Diagnosis

- Incubation period in a patient with toxigenic diarrhoea (usually associated with vomiting) is shorter (2–12 hours) as compared to that in inflammatory diarrhoea.
- Sudden onset in toxic diarrhoea while it is subacute in inflammatory diarrhoea.
- Presence of fever, severe abdominal tenderness or tenesmus suggest inflammatory colitis.
- Vomiting developing suddenly along with diarrhoea indicates toxin-mediated event. However, if other associated features like headache and fever are present, infection is likely.
- Diarrhoea with blood suggests *Shigella*, *E. coli* or *E. histolytica* infection.
- If patient is previously on an antibiotic, consider *Cl. difficile* infection.
- Outbreaks indicate toxigenic GE.
- If stool does not have leucocytes, consider toxin-induced causes. If leucocytes are present or the illness continues, consider inflammatory causes (*Shigella*, *Salmonella*, *Campylobacter*, *E. coli*, *Entamoeba* and *Cl. difficile*).

Small Bowel versus Large Bowel Diarrhoea

- Small bowel diarrhoea
  - Characterised by a large-volume and watery diarrhoea
  - Associated abdominal cramping, bloating and gas formation is present
  - Fever uncommon
  - No tenesmus
  - No inflammatory cells in stools
- Large bowel diarrhoea
  - Frequent, small volume, often painful bowel movements with tenesmus
  - Fever and stools with blood or mucus are common
  - Gripping pain in lower abdomen
  - Red blood cells and inflammatory cells in the stool

Management

- Most cases are self-limiting and require fluid therapy only.

Rehydration

- Toxin-induced diarrhoea produces stools that are nearly isotonic. Sodium and chloride concentrations are slightly less than those in plasma, while bicarbonate concentration is double that of plasma. The stools also contain significant amount of potassium.
- In inflammatory diarrhoea the electrolyte loss is of less magnitude compared to toxigenic diarrhoea.
- Oral rehydration solution (ORS)
  - Exploits absorption of glucose-coupled sodium, which remains intact even in severe diarrhoea.
  - Traditionally, ORS was prepared by adding 3.5 g of sodium chloride (three-fourth teaspoon of salt), 2.5 g of sodium bicarbonate (1 teaspoon of baking soda) or 2.9 g of sodium citrate, 1.5 g of potassium chloride (1 cup of orange juice or two bananas) and 20 g of glucose (4 teaspoon of sugar) to a litre of boiled water. Final solution contains 90 mmol of sodium, 20 mmol of potassium, 80 mmol of chloride, 30 mmol of bicarbonate and 111 mmol of glucose/L (osmolarity 331 mOsm/L).
  - Presently, ORS of lower osmolarity is used as it reduces stool output and vomiting, and also the need for intravenous rehydration as compared to standard ORS. It contains 13.5 g of glucose, 2.6 g of sodium chloride, 1.5 g of potassium chloride and 2.9 g of trisodium citrate with final concentrations of sodium 75 mmol/L, chloride 65 mmol/L, potassium 20 mEq/L, glucose 75 mmol/L and citrate 10 mmol/L with an osmolarity of 245 mOsm/L.
- Intravenous fluids
  - For moderate to severe dehydration.
  - Normal saline not ideal as it has no potassium and bicarbonate.
  - Ringer's lactate is usually administered.
  - In severe cases fluids at a rate of 20 mL/kg/hour for the first 2–3 hours are administered. If the patient improves, reduce the rate to 10 mL/kg/hour for the next 2-4 hours.
  - Start concurrent oral rehydration therapy.

Early Feeding

- Early refeeding decreases intestinal permeability caused by infections, reduces illness duration and improves outcomes.

Adsorbents

- Kaolin may be useful in some patients as it adsorbs the toxin.
- Does not influence the course of the disease.

Antimotility Drugs

- Consider these agents for symptomatic treatment of toxin-induced diarrhoea in adults only.
- Can be given in inflammatory, non bloody diarrhoea along with antibiotics.
- Should not be used in young children and elderly.
- Various agents are:
    - Opiates (e.g. morphine and codeine). May produce respiratory depression.
    - Diphenoxylate/atropine combination. May produce respiratory depression and anticholinergic side effects.
    - Loperamide has the fewest side effects of all antimotility agents. Dose is 2 tablets of 4 mg each initially, then 2 mg after each unformed stool, not to exceed 16 mg/day for ≤2 days.
    - Bismuth subsalicylate acts as an antisecretory agent and can provide effective clinical relief without significant side effects. Dose is 1 tablet every 30 minutes for a total of 8 doses or 60 mL every 6 hourly.

Antisecretory Agents

- Racecadotril
    - Decreases hypersecretion of water and electrolytes into the intestinal lumen
    - Inhibits enkephalinase, an enzyme that degrades enkephalins
    - Dose is 100 mg TID
    - Should be used in patients with acute and watery diarrhoea only
    - Contraindicated in renal insufficiency, pregnancy and breast feeding

Antispasmodics

- Mild antispasmodics (dicyclomine and hyoscine) in patients with significant abdominal cramps.

Antibiotics

- Antibiotics may be used in the following situations:
    - Symptomatic patients with inflammatory diarrhoea (high fever, toxicity and abdominal pain)
    - Patients presenting with an acute febrile dysentery illness.
    - Diarrhoea ocurrs due to *Campylobacter jejuni,* where early use of erythromycin or azithromycin limits the duration of illness
- If clinical presentation suggests a possibility of Shiga toxin–producing *E. coli* (e.g. bloody diarrhoea), antibiotics should be avoided because they may increase the risk of haemolytic uraemic syndrome.
- Commonly used antibiotics are quinolones (norfloxacin 400 mg and ciprofloxacin 500 mg, both given twice daily or levofloxacin 500 mg given once a day) for 3–5 days.
- In patients with suspected cholera, administer doxycycline in a dose of 300 mg as a single dose. Alternatives include trimethoprim–sulphamethoxazole, furazolidone and norfloxacin.

Probiotics

- Probiotics are commonly recommended by physicians to limit the duration of diarrhoea. These agents are used along with ORS.

Zinc

- In children older than 6 months, zinc supplementation helps in treating and preventing acute diarrhoea.

Q. What are the causes of chronic blood and mucus in the stools? Mention the investigations done in such cases. Stress the importance of stool examination in such a case.

Causes

• Amoebic dysentery	• Carcinoma of the lower large bowel—rectum, sigmoid and colon
• Bacillary dysentery	• Diverticulitis
• Ulcerative colitis	• Necrotising enterocolitis
• Crohn's disease	• Mesenteric vascular disease
• Intestinal tuberculosis	

Investigations

- Stool
    - Macroscopy
        - Fresh blood? Altered blood? Sticky? Foul smelling? Bulky? Floats in water? Mucus?

- Microscopy
  - Ova
  - Cysts
  - Trophozoites
  - Bacteria
  - Pus cells
  - Red blood cells
  - Macrophages
  - Culture and sensitivity—grows the organism.
- Proctoscopy—detects ulcers and tumours of rectum and pile masses.
- Sigmoidoscopy—visualises sigmoid colon, detects ulcers and tumours.
- Colonoscopy—visualisation of colon.
- Barium enema—detects growths or filling defects, strictures, ulcers and diverticulae.
- Biopsy—of an ulcer or growth can be done using sigmoidoscope or colonoscope.

Q. Write a short note on occult blood in the stool.

- Patients with gastroduodenal bleeding of up to 60–100 mL per day may have normal-appearing stools (i.e. no melaena).
- Faecal blood loss in normal individuals varies from 0.5 to 1.5 mL per day; most faecal occult blood tests begin to become positive at a level of around 2 mL of blood loss per day.
- Occult blood in stools is detected by guaiac test—should be performed for several successive days because bleeding from the gastrointestinal tract is often intermittent. Unlike previous belief, this test is negative in a person on iron or bismuth.
- Other tests include faecal immunochemical tests and haeme–porphyrin test.

Conditions where Occult Blood is Positive

- Upper gastrointestinal bleeding—peptic ulcer, malignancy, gastritis, oesophagitis, varices
- Lower gastrointestinal bleeding—malignancy, haemorrhoids, diverticulitis, inflammatory bowel disease, coeliac sprue
- Hookworm disease
- Some patients on aspirin or steroids (rare)
- Mesenteric vascular disease
- Investigations include colonoscopy, oesophago gastroduodenoscopy, enteroscopy, capsule endoscopy, enteroclysis, radionuclide studies, CT abdomen and angiography

Q. What are the causes of haematemesis? Discuss the management of a patient with upper gastrointestinal bleeding.

- Upper gastrointestinal (UGI) bleeding indicates bleeding proximal to the duoden–jejunal junction (ligament of Treitz).
- Presents with haematemesis, melaena or both.

Aetiology

Oesophageal causes	• Peptic ulcer (gastric and duodenal)
• Oesophageal varices	• Gastric carcinoma
• Oesophagitis	
• Oesophageal carcinoma	**Miscellaneous causes**
• Mallory-Weiss syndrome	• Rupture of aortic aneurysm
	• Coagulation defects
Gastroduodenal causes	• Angiodysplasia or vascular malformations
• Erosive gastritis or duodenitis	
• Stress ulcers	

- Erosive gastritis
  - Can occur after ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) and alcohol.
  - Can occur due to stress like trauma, burns, sepsis and shock.
- Variceal bleeding usually occurs from the lower 5 cm of oesophagus.
- Mallory–Weiss syndrome is an uncommon cause of UGI bleeding. It results from a linear tear in the distal oesophagus and proximal stomach. An episode of forceful retching precedes the onset of bleeding in most cases.

Clinical Features

- The patient most often presents with haematemesis and/or melaena.
- Colour of the vomitus depends on how long the blood has been in the stomach; bright red blood suggests a rapid and sizeable haemorrhage, while "coffee ground" colour is consistent with a small bleed.
- Melaena indicates black tarry stools. It occurs when more than 60 mL blood is lost into the upper gastrointestinal tract.
- Passage of frank blood per rectum (haematochezia) in massive bleed.
- Occasionally, presentation with symptoms of blood loss only. These include dizziness, extreme pallor, shock, angina or syncope.

Features Suggesting Severe Bleeding

• Presence of clots in the vomitus	• Hypotension and tachycardia
• Fresh blood in the nasogastric aspirate	• A fall in systolic blood pressure >10 mmHg and a rise in pulse rate of >20 beats/minute on change of posture from lying to sitting position
• Haematochezia	

Diagnosis

- History of alcohol or drug (NSAIDs) ingestion, trauma, burns or sepsis suggests bleeding from gastric erosions.
- History of use of other drugs like antiplatelet agents (aspirin, clopidogrel) and anticoagulants indicates coagulation defect.
- A history suggestive of peptic ulcer (even though many patients with peptic ulcer may not give such history).
- History of jaundice, pedal oedema, abdominal distension, and presence of splenomegaly, ascites, dilated abdominal veins or other features of liver cell failure (spider nevi, palmar erythema, jaundice and gynaecomastia) suggest variceal bleed.
- Haematemesis preceded by retching and a blood free vomitus suggests a Mallory–Weiss tear.
- History of dysphagia and weight loss prior to bleed suggests a malignant cause.

Investigations

- Type and cross match of blood, haemoglobin and haematocrit, blood urea and creatinine, coagulation profile, platelet count, and liver function tests. An elevation of blood urea is associated with upper GI bleed. In the absence of renal failure, a blood urea to creatinine ratio of more than 72 indicates upper GI bleed rather than a lower GI bleed.
- ECG, if suspicion of acute coronary syndrome.
- Nasogastric aspirate.
- Upper GI endoscopy.
- Angiography.

Management

- In case of massive bleeding, resuscitate and replenish intravascular volume with fluids and blood before any diagnostic measures and other therapeutic measures. Aim at maintaining haemoglobin above 7–8 g/dL.
- Assess the pulse, blood pressure, postural hypotension, urine output and level of consciousness.
- Blood for grouping and cross matching and other investigations.

Gastric Lavage

- Perform a gastric lavage by instilling 500 mL of ice-cold or tap water (both are equally effective) every 30–60 minutes.
- Do not apply vigorous suction for aspiration as it may produce further mucosal damage that may interfere with interpretation of endoscopic findings.
- Addition of noradrenaline in the lavage fluid does not give additional benefit over tap water.
- Lavage leads to at least temporary cessation of bleeding in 80–90% of patients.
- Nasogastric tube should be kept for 24 hours after cessation of bleed to facilitate detection of rebleed.
- Gastric aspiration helps to:
  - Assess the rate of bleeding.
  - Clear the stomach prior to endoscopy.
  - Remove blood, thereby reducing the risk of encephalopathy in patients with liver disease.
  - Dilute acid pepsin in stomach thereby reducing bleeding from erosions.

Endoscopy

- Upper GI endoscopy as soon as the patient is haemodynamically stable. If bleeding has stopped, it can be postponed by a few hours. It helps in:
  - Early diagnosis.
  - Identifying patients who may rebleed.
  - Treatment of underlying condition (e.g. sclerotherapy in oesophageal variceal bleed).
- Features indicating a high risk of rebleed from varices:
  - Large-sized varices
  - Presence of daughter varices
  - Presence of cherry red spots over the varices
- Features indicating a high risk of rebleed from peptic ulcer:
  - Presence of a sentinel clot over the ulcer
  - Presence of exposed blood vessel (non-bleeding blood vessels) at the base of the ulcer

Other Investigations

- Angiography or radionuclide scan to delineate the anatomical site of bleeding, if endoscopy fails.

Other Management Strategies

Proton-Pump Inhibitors

- Omeprazole 40–80 mg intravenously followed by 8 mg/hour infusion
- Pantoprazole 40 mg intravenously followed by 8 mg/hour infusion

Fresh Frozen Plasma and Platelets

- Fresh frozen plasma in patients with active bleeding and coagulopathy
- Platelet transfusion in patients with active bleeding and thrombocytopenia

Balloon Tamponade, Vasopressin, Octreotide

- Discussed under "variceal bleed".

Endoscopic Therapeutic Measures

- Thermal measures
  - These include use of lasers, argon plasma coagulation, electrocoagulation and heater probe thermocoagulation.
- No-thermal measures
  - Endoscopic band ligation of bleeding vein and application of an arterial clip
  - Endoscopic sclerotherapy (EST)
  - Injection of dilute (1:10,000) adrenaline in 1 mL aliquots around bleeding points along with fibrin glue

Antifibrinolytic Drug

- Tranexamic acid may be used in selected patients

Radiological Measures

- Embolisation of the bleeding artery using autologous clot, gel foam or metallic coil may be effective in some patients in whom angiography is able to localise the site of bleed.

Surgical Measures

- If variceal bleed cannot be controlled with medical measures, emergency surgery is required. This includes shunt surgery or *transaction–devascularisation* of oesophageal varices.
- In patients with bleeding ulcer, surgery is contemplated, if bleeding cannot be controlled with medical measures or if patient rebleeds after initial control.
- In patients with gastric erosions, total gastrectomy or vagotomy with drainage is required, if medical measures fail.

Q. List down the common causes of weight loss.

- Weight loss is defined as loss of more than 5% of usual body weight over six months.

Causes of Weight Loss

- Diabetes mellitus
- Endocrine diseases—hyperthyroidism, phaeochromocytoma, panhypopituitarism, adrenal insufficiency
- Gastrointestinal causes—tropical sprue, chronic pancreatitis, chronic diarrhoea due to ulcerative colitis and Crohn's disease, parasitic infestations, malabsorption
- Infections—tuberculosis, fungal infections, amoebic abscess, bacterial endocarditis, HIV
- Malignancy—any occult malignancy, stomach, pancreas, liver, lymphoma, leukaemia
- Psychiatric—anorexia nervosa, depression, schizophrenia
- Renal disease—chronic renal failure
- Drugs—anticonvulsants, antidepressants, levodopa, digoxin, metformin, exenatide, liraglutide
- Miscellaneous—chronic obstructive pulmonary disease (pulmonary cachexia), chronic cardiac failure (cardiac cachexia), dementia, Parkinson's disease, motor neuron disease

Q. What are the causes of glossitis?

- Glossitis is inflammation of the tongue and denotes soreness and redness of the tongue.

Causes

- B-complex deficiency, megaloblastic anaemia, cirrhosis, pernicious anaemia, iron deficiency anaemia, pellagra, scarlet fever, syphilis, gonorrhoea and tuberculosis.

Q. What are the causes of dysphagia? How will you investigate a case of dysphagia?

- Dysphagia is defined as a subjective sensation of difficulty or abnormality of swallowing.
- Odynophagia is defined as pain, while swallowing.

I. Congenital
- Congenital stenosis of oesophagus
- Tracheo-oesophageal fistula
- Congenital web

II. Acquired
- A. Causes within the oesophageal lumen
  - Foreign body
- B. Causes in the oesophageal wall
  - Strictures
  - Carcinoma oesophagus
  - Diverticulum
  - Reflux oesophagitis
  - Achalasia cardia
  - Plummer–Vinson syndrome
  - Oesophagitis (cytomegalovirus, herpes simplex, varicella-zoster, candida)
  - Diffuse oesophageal spasm
  - Chagas disease

- C. Causes outside the oesophageal wall
  - Thyroid swelling
  - Secondaries in the neck
  - Mediastinal nodes
  - Mediastinal abscess
  - Aortic aneurysm
- D. Painful diseases of mouth and pharynx
  - Stomatitis
  - Tonsillitis
  - Pharyngitis
  - Retropharyngeal abscess
- E. Neuromuscular disorders
  - Bulbar paralysis
  - Myasthenia gravis
  - Polymyositis
- F. Miscellaneous
  - Sjogren's syndrome
  - Rabies
  - Tetanus

- In general, mechanical causes commonly lead to dysphagia for solid foods initially, whereas patients with motility disorders tend to complain of progressive or nonprogressive dysphagia for both liquids and solids from the onset.

Investigations

- Haemoglobin and peripheral smear for anaemia
- Chest radiograph detects retrosternal goitre, mediastinal lymph nodes, aortic aneurysms, primary and secondary malignancy of lungs
- Barium swallow detects tumours as filling defects or strictures (rat tail appearance)
- Oesophagoscopy allows removal of foreign body, visualisation and biopsy of tumours, ulcers, strictures, etc.
- CT scan of thorax

- Biopsy from the growth, ulcer or inflamed mucosa
- Oesophageal motility studies (oesophageal manometry)

Q. Briefly describe about Plummer–Vinson syndrome (Patterson–Kelly syndrome).

Q. Write a short note on sideropenic dysphagia.

- A syndrome characterised by:
  - Dysphagia to solids
  - Iron deficiency
  - Koilonychia
  - Glossitis
- Dysphagia is due to a thin web in the postcricoid area. The web is formed of degenerated epithelial cells.
- Usually seen in postmenopausal females.
- Increased risk for developing squamous cell carcinoma of upper gastrointestinal tract.
- Investigations:
  - Haemoglobin and PCV low.
  - Peripheral smear shows microcytic hypochromic anaemia.
  - Serum iron is low and iron binding capacity is increased.
  - Bone marrow iron stores are depleted.
  - Barium swallow may show the web.
  - Videofluoroscopy and endoscopy better than barium swallow.
- Treatment:
  - Treatment of iron deficiency anaemia with iron may be effective in resolving dysphagia.
  - Endoscopic dilatation.
  - Follow-up endoscopy at periodic intervals to detect development of carcinoma.

Q. What is gastro-oesophageal reflux disease (GERD; reflux oesophagitis)? What are the normal mechanisms preventing reflux? Give the causes, clinical features, investigations, complications and treatment of reflux oesophagitis.

- Several mechanisms operate to prevent the reflux of gastric contents into the oesophagus. When these mechanisms fail gastric contents reflux into the lower oesophagus. Reflux that causes troublesome symptoms or mucosal injury in the oesophagus is called gastro-oesophageal reflux disease (GERD).
- Reflux oesophagitis occurs when the mucosal defences are unable to counteract the damage produced by refluxed acid, pepsin and bile.
- Severe oesophagitis can produce ulceration, bleeding and later on, peptic stricture.
- In long-standing oesophagitis the lower oesophageal mucosa may change from squamous to columnar type (Barrett's mucosa). Barrett's mucosa is susceptible to ulcers, strictures and malignant changes (adenocarcinoma of oesophagus).

Mechanisms Preventing Reflux and Reflux Oesophagitis

- Lower oesophageal sphincter (LES), at the lower end of oesophagus below the diaphragm. It is a 3–4 cm segment of tonically contracted circular smooth muscle at the distal end of the oesophagus
- Striated muscles of the diaphragmatic crura
- Anatomical flap valve at oesophagogastric junction. It keeps the distal part of LES in the abdomen and to maintains the angle of His (see below)
- Intra-abdominal pressure reinforces the LES tone
- Oblique entry of oesophagus to the stomach (angle of His)
- Secondary peristaltic waves in the oesophagus clear the refluxed material
- Swallowed saliva neutralises the refluxed acid

Causes

- Sliding hiatus hernia—In this type of hernia the oesophagogastric junction slides up through the diaphragm. This results in:
  a. Loss of the obliquity of entry of oesophagus into stomach.
  b. Loss of the reinforcing effect of intra-abdominal pressure on the LES (refer above).
     - These two factors facilitate gastro-oesophageal reflux.
     - So hiatus hernia facilitates gastro-oesophageal reflux but does not directly cause it.
- Cardiomyotomy and vagotomy reduce the efficiency of the LES.

- Pregnancy, obesity, ascites, weight lifting and straining act by increasing the intra-abdominal pressure.
- Cigarette smoking, alcohol, fatty foods and caffeine act by reducing the lower oesophageal sphincter tone.
- Impaired gastric emptying due to gastric outlet obstruction, anticholinergic drugs and fatty food act by increasing the gastric content available for reflux.
- Large volume meals act by the above mechanism.
- Systemic sclerosis.
- Drugs (aminophylline, β-agonists, nitrates, calcium channel blockers) that reduce the tone of LES.
- Acid pocket—In postprandial period, a layer of unbuffered acidic gastric juice sit on top of the meal, close to the cardia; this is known as acid pocket. A more proximal location of acid pocket is seen in patients with GERD.
- Hypersensitivity to acid reflux.

Helicobacter pylori

- *Helicobacter pylori*, a spiral-shaped bacterium located in the mucous layer of the stomach, may inhibit or exacerbate acid reflux depending on how the infection affects the stomach.
- Distal gastritis increases the production of gastric acid. In this condition, the eradication of *H. pylori* not only reduces the risk of peptic ulceration but also the risk of acid reflux.
- Conversely, generalised atrophic gastritis decreases the production of gastric acid; as a result *H. pylori* eradication may increase the severity of reflux.
- Since chronic *H. pylori* infection is associated with an increased risk of peptic ulceration and gastric cancer, *H. pylori* eradication is recommended even though *H. pylori* does not have an important role in pathogenesis of GERD.

Clinical Features

- Heartburn (pyrosis) is deeply placed burning pain behind the sternum radiating to the throat. It occurs after meals, brought on by bending, lifting weight and straining. Heartburn occurs on lying down in bed at night and is then relieved by sitting up.
- Regurgitation of gastric contents into the mouth (acid eructation) without associated nausea or retching.
- Tracheal aspiration with coughing or laryngismus or aspiration pneumonia results from the regurgitated gastric contents in the mouth.
- Odynophagia—painful swallowing.
- Transient dysphagia to solids due to oesophageal spasm.
- Persistent dysphagia to solids due to strictures or development of oesophageal carcinoma.
- Iron deficiency anaemia due to blood loss.
- Extraoesophageal symptoms include hoarseness, sore throat, sinusitis, otitis media, chronic cough, laryngitis, non-atopic asthma, recurrent aspiration and pulmonary fibrosis.

Complications

• Oesophagitis	• Strictures
• Oesophageal ulcers	• Aspiration pneumonia
• Barrett's oesophagus	• Iron deficiency anaemia
• Carcinoma oesophagus	

Alarming Symptoms

• Weight loss	• Dysphagia
• GI bleeding	• Odynophagia
• Nausea and vomiting	• Family history of cancer

Investigations

- Endoscopy
  - Oesophagitis can be visualised and confirmed by biopsy.
  - Strictures can be visualised.
  - Barrett's mucosa can be confirmed by biopsy.
- Barium swallow and meal can reveal a hiatus hernia.
- Ambulatory oesophageal pH metry may reveal a sudden decrease in intraoesophageal pH from above to below 4.0. Wireless capsule is also available for oesophageal pH recording.
- Bernstein test is done in patients with high clinical suspicion but negative endoscopy. Perfusion of acid into the lower oesophagus may reproduce the symptoms.
- Resting ECG and stress ECG to rule out ischaemic heart disease.

- Oesophageal motility studies (primarily done before surgical intervention to exclude achalasia and other motility disorders and not for diagnosis of GERD).

Treatment

- General measures
  - Weight reduction and cessation of smoking.
  - Small volume, frequent feeds.
  - Avoid alcohol, fatty food, caffeine, mint, orange juice, some medications. Avoid late night meals.
  - Avoid weight lifting, stooping and bending at waist. Head end of the bed should be elevated to 15°.
- Medical treatment
  - Liquid antacid 10–15 mL, 1 and 3 hours after meal relieves heart burn (in mild cases). Treatment with alginate-antacid preparations abolishes acid pocket and helps in reducing GERD.
  - H_2-receptor antagonists like cimetidine 400 mg or ranitidine 150 mg, 2–4 times daily with meals and before bed time, for at least 6 weeks (in mild cases).
  - Proton-pump inhibitors (PPIs) in moderate to severe cases: These include omeprazole (20–40 mg/day), lansoprazole (15–30 mg/day), pantoprazole (40 mg/day), esomeprazole (40 mg/day), rabeprazole (10–20 mg/day) and ilaprazole (10 mg/day). The most common side effects are headache, diarrhoea, abdominal pain and nausea. These are useful in moderate to severe cases, and are given for 6–8 weeks in higher doses. Maintenance doses may be required for 6–8 months.
  - Metoclopramide or domperidone 10 mg thrice daily increases the LES tone and promotes gastric emptying.
  - Other prokinetics include mosapride, itopride and levosulpiride.
  - Therapy for *H. pylori* if infection is evident on serology or urea breath test. It improves histologic signs of gastric inflammation but does not improve symptoms or rates of recurrence of GERD.
  - Oesophageal stricture is treated by repeated dilatations.
  - Oral iron or blood transfusion for anaemia.
- Surgical treatment
  - Surgical resection of strictures.
  - Surgical return of LES to the abdomen and construction of an additional valve mechanism (fundoplication) for sliding hiatus hernia.

Q. Give a brief account of sliding hiatus hernia.

- A hiatal hernia is herniation of part of stomach into the thoracic cavity through the diaphragm. In sliding hiatus hernia, gastro-oesophageal junction and the fundus of stomach slide upward.
- Aetiology
  - Unknown
  - Obesity, pregnancy and ascites may be aetiological factors.
  - Occurs in 33% of normal adults and 50% of elderly.
- Clinical features
  - Majority are asymptomatic.
  - Hiatus hernia predisposes to gastro-oesophageal reflux, and hence, symptoms of reflux may be present.
  - Complications include volvulus of stomach, bleeding from gastric ulcer, gastritis or gastric erosions and respiratory complications from mechanical compression of the lung by a large hernia.
- Investigations
  - Chest X-ray may show fundal air-fluid level in chest.
  - Barium swallow will demonstrate the presence of gastro-oesophageal junction in the thorax.
  - Endoscopy.
- Management
  - Asymptomatic hiatus hernias do not require any treatment.
  - If gastro-oesophageal reflux is present, surgical repair of hernia is done in selected cases. Surgery involves repair of the diaphragmatic defect, and fixing the stomach in the abdominal cavity (fundoplication) combined with an antireflux procedure.

Q. Discuss the aetiopathogenesis, clinical features and management of acid peptic disease or peptic ulcer disease.

Q. Briefly describe about *Helicobacter pylori*.

- Peptic ulcer refers to an ulcer in the lower oesophagus, stomach or duodenum, in the jejunum after surgical anastomosis to stomach, and in the ileum adjacent to a Meckel's diverticulum.

- Incidence—10% of all adult males.
- Approximately 90% of peptic ulcers are caused by *Helicobacter pylori* infection or nonsteroidal anti-inflammatory drug (NSAID) use.

Aetiopathogenesis

- Heredity
  - Strong family history with gastric ulcers, but less strong family history with duodenal ulcers.
- Acid pepsin versus mucosal resistance.
  - Cause of peptic ulceration is digestion of the mucosa with acid and pepsin of gastric juice. Normal stomach is capable of resisting this digestion. So, the concept of peptic ulceration is acid plus pepsin versus mucosal resistance. Factors that tilt this balance produce ulcers.
  - Gastric hypersecretion
    - Ulcers occur only in the presence of acid and pepsin. Severe ulceration occurs in Zollinger–Ellison syndrome, which is characterised by very high acid secretion. Acid secretion is more important in the aetiology of duodenal ulcer than in gastric ulcer.
  - Mucosal resistance
    - Several mechanisms protect gastric mucosa from the acid.
      - Surface epithelial cells secrete bicarbonate under the influence of mucosal prostaglandins, and this bicarbonate neutralises the acid.
      - The surface cells are also secrete mucus that impedes the diffusion of ions and molecules such as pepsin.
      - The tight intercellular junctions and the surface lipoprotein layer provides a mechanical barrier.
      - Normal turnover of epithelial cells has a protective function. In addition, migration of epithelial cells bordering site of injury restore a damaged region.
      - The submucosal area provides adequate micronutrients and oxygen while removing toxic metabolic byproducts of gastric epithelial cells.
  - Collectively, these mechanisms can be described as the "gastric mucosal barrier".
  - Prostaglandins plays a central role in mucosal resistance. They regulate the release of mucosal bicarbonate and mucus, inhibit parietal cell secretion and are important in maintaining mucosal blood flow. This explains the ulcerogenic properties of NSAIDs.
  - Factors reducing mucosal resistance.
    - Several drugs, particularly those used in rheumatoid arthritis.
    - Aspirin is an important aetiological factor in gastric ulcer. It damages the membrane and tight junctions. It also inhibits prostaglandin synthesis, thus reducing bicarbonate secretion.
    - The organism *Helicobacter pylori*.
    - Reflux of bile and intestinal contents into stomach, due to poorly functioning pyloric sphincter.
- Other risk factors include smoking and alcohol consumption.

Helicobacter pylori

- Majority of gastric and duodenal ulcers can be attributed to NSAIDs and *H. pylori*.
- *H. pylori* also plays a role in the development of gastritis, MALT (mucosal-associated lymphoid tissue) lymphoma (extranodal marginal zone B-cell lymphoma of MALT type; most common site is stomach), gastric adenocarcinoma, gastritis and dyspepsia.
- *H. pylori* is a gram-negative bacillus that produces mucosal damage.
- In a developing country, nearly 80% of persons are colonised with it by the age of 20 years. Other risk factors for acquiring *H. pylori* infection include poor socio economic conditions and family overcrowding.
- Transmission occurs following oral–oral or faeco–oral route.
- Postulated mechanisms for ulcer development:
  - Key factors secreted by the bacillus is urease (which converts urea into ammonia, thus alkalinising the surrounding acidic medium for its survival but simultaneously producing ammonia-induced mucosal damage. Production of ammonia by bacteria prevents D cells in the antral glands from sensing the true level of acidity, leading to inappropriate release of somatostatin and an increase in gastrin, and consequently excess acid secretion.
  - Neural pathways are also affected by *H. pylori*, which results in down regulation of acid production.
  - *H. pylori* causes an inflammatory response in gastric mucosa, with induction of epithelium-derived cytokines (interleukin 8 and interleukin 1β). Influx of neutrophils and macrophages into the gastric mucosa with release of lysosomal enzymes, leukotrienes and reactive oxygen species impairs mucosal defence.
  - Inflammatory response is also results in release of additional factors with ulcerogenic potential, including platelet-activating factor and complement factors.

Aetiology of Acute and Stress Ulcers

- Aspirin
- Head injury, burns, severe sepsis, surgery and trauma lead to peptic ulceration known as stress ulcers.
  - Head injury causes ulcers by gastric hypersecretion (Cushing's ulcer).
  - Burns and shock produce ulcers by reflux of duodenal contents and mucosal ischemia.

Clinical Features

- Peptic ulcer is a chronic condition with a natural history of spontaneous relapses and remissions lasting for decades or even life.
- The most common presentation is that of recurrent abdominal pain that has three notable characters:
  - Localisation to the epigastrium
  - Relationship to food
  - Periodicity
- Epigastric pain
  - Pain is referred to epigastrium and is so sharply localised that the patient will localise the site with one finger (pointing sign). It is usually burning in character.
- Hunger pain
  - Pain occurs on empty stomach (hunger pain) and is relieved by food or antacids.
- Night pain
  - Typically, the pain wakes the patient from sleep around 3 am and is relieved by food, milk or antacids.
- Pain relief
  - Pain is usually relieved by food, milk, antacids, belching or vomiting.
  - In some patients with gastric ulcer, food may precipitate the pain.
- Periodicity (episodic pain)
  - Pain occurs in episodes, lasting 1–3 weeks every time, three to four times a year. Between episodes patient is perfectly well.
  - In the initial stages, the episodes are short in duration and less frequent. As the natural history evolves the episodes become longer in duration and more frequent.
  - Patients are more symptomatic during winter and spring.
  - Relapses are more common in smokers than in non-smokers.
- Other symptoms
  - Water brash (excessive salivation), heart burns, loss of appetite and vomiting.
  - Anorexia, nausea, fullness, bloating and dyspepsia.
  - Rarely, the patient might present for the first time with anaemia of chronic blood loss, abrupt haematemesis, acute perforation or gastric outlet obstruction.

Differences between Gastric Ulcer and Duodenal Ulcer

Factors	Gastric ulcer	Duodenal ulcer
Age	More than 40 years	20–50 years
Sex	Equal in both sexes	More in males
Course of the illness	Less remittent	More remittent
Episodes of pain	Relatively longer in duration	Relatively shorter in duration
Antacids	Relief of pain not consistent	Relief of pain prompt
Food	Provokes the pain	Relieves the pain
Heart burn	Less common	More common
Night pains	Less common	More common
Anorexia and nausea	More common	Less common

Complications

- Upper gastrointestinal bleed
- Perforation
- Gastric outlet obstruction (with fluid and electrolyte imbalance)
- Gastric malignancy
- Pancreatitis (due to posterior penetration of ulcer)

Investigations

- Double contrast barium meal may show the ulcer as a crater or as a deformed duodenal cap.
- Endoscopy can visualise the ulcer. Typical location is duodenal bulb and lesser curvature of stomach. A biopsy can be taken from a gastric ulcer to rule out malignancy (10% of gastric ulcers are malignant) and *H. pylori* infection.
- Tests for *H. pylori*.
- Serum gastrin and gastric acid analysis in patients suspected to have Zollinger–Ellison syndrome.

Tests for H. pylori

On endoscopic biopsy material
- Rapid urease test (false negative with recent use of proton pump inhibitors, antibiotics)
- Histology (sensitivity reduced with use of proton pump inhibitors, antibiotics and bismuth-containing compounds)
- Culture (technically demanding)

Non-invasive
- Serology for immunoglobulin G (positive results may persist for months after eradication)
- Urea breath test (false negative with recent use of proton pump inhibitors, antibiotics)
- *H. pylori* stool antigen test (test for cure 7 days after therapy is accurate; sensitivity is reduced with use of proton pump inhibitors, antibiotics and bismuth containing compounds)

Treatment

- Short-term management
- Long-term management
  - Intermittent treatment
  - Maintenance treatment
  - Surgical treatment

Short-Term Management

I. General Measures

- Avoid smoking
- Avoid aspirin and NSAIDs
- Alcohol to be moderated
- No special dietary advice though patients should avoid any foods that precipitate symptoms

II. Antacids

- Mainly prescribed for symptomatic relief only
- Act by neutralising acidity
- Minor pain is treated with tablet preparations and severe pain with liquid preparations
- Dose is 15–30 mL liquid antacid 1 and 3 hours after food and at bedtime for 4–6 weeks. Rarely used at present.
- Commonly used antacids are a combination of aluminium and magnesium compounds, sodium bicarbonate and calcium carbonate.

Side Effects

- Aluminium compounds cause constipation, phosphate depletion and block the absorption of digoxin and tetracycline.
- Magnesium compounds cause diarrhoea, hypercalcaemia and hypermagnesaemia.
- Calcium compounds cause constipation, hypercalcaemia and milk-alkali syndrome (hypercalcaemia, alkalosis, and renal impairment).
- Bicarbonate preparations cause alkalosis.
- All antacids contain significant sodium, which will lead to water retention and hence, exacerbation of cardiac failure and ascites.

III. Histamine H$_2$-receptor Antagonists

- Include cimetidine, ranitidine, famotidine and nizatidine.
- All the four are equally effective.
- The mechanism of action is inhibition of acid and pepsin secretion by blocking H$_2$-receptors.
- Can be prescribed as twice daily doses or as a single large dose at bedtime.

- Symptomatic relief occurs within days and ulcer healing within weeks.
- Duration of treatment of duodenal ulcer patients is 4 weeks. In smokers and in patients who have had recent major complications (haematemesis and perforation) treatment should be prolonged to 6–8 weeks.
- Gastric ulcer patients are treated for 6 weeks, followed by endoscopy and further treatment, if necessary. A gastric ulcer that has not healed by 12 weeks should be treated with omeprazole or surgery.

Cimetidine

- 400 mg BD or 800 mg at night.
- Side effects include gynaecomastia in males, confusion in elderly, oligospermia, delay in elimination of warfarin, phenytoin and theophylline.

Ranitidine

- 150 mg BD or 300 mg at night.
- Side effects are confusion and liver dysfunction.

Famotidine

- 20 mg BD or 40 mg at night.
- Side effects are headache, dizziness and dry mouth.

Nizatidine

- 150 mg BD or 300 mg at night.
- Side effects are sweating, urticaria and somnolence.

IV. Proton Pump Inhibitors

- These are substituted benzimidazoles and include omeprazole, lansoprazole, pantoprazole, esomeprazole, rabeprazole and ilaprazole.
- Omeprazole, lansoprazole and esomeprazole should be taken 30 minutes before a meal.
- Rabeprazole and pantoprazole may be taken without regard to meals.

Mechanism of Action

- PPIs cross the parietal cell membrane and enter the acidic parietal cell canaliculus.
- In the acidic environment, the PPI becomes protonated, producing the activated form of the drug that binds covalently with the $H1/K+$ ATPase enzyme that results in irreversible inhibition of acid secretion by the proton pump.
- The parietal cell must then produce new proton pumps or activate resting pumps to resume its acid secretion.

Efficacy in Peptic Ulcer Disease

- PPIs have superior healing rates, shorter healing time and faster symptom relief compared to H_2-blockers.
- All PPIs appear to have similar efficacy in the treatment of various acid peptic disorders.

Side Effects

- The most common side effects are headache, diarrhoea (including pseudomembranous colitis produced by *Clostridium difficile*), abdominal pain and nausea.
- Other possible effects include B_{12}, iron and calcium malabsorption, osteoporosis and related fractures and interaction with some drugs (reduce absorption of ketoconazole and increase absorption of digoxin).
- Omeprazole and esomeprazole reduce effectiveness of clopidogrel by interfering with its metabolism to active metabolite.

Drug Interactions

Drug	Omeprazole	Lansoprazole	Pantoprazole	Rabeprazole
Carbamazepine	↓ Metabolism	Unknown	None	Unknown
Diazepam	↓ Metabolism	None	None	None
Digoxin	↑ Absorption	Unknown	↑ Absorption	↑ Absorption
Ketoconazole	↓ Absorption	↓ Absorption	Unknown	↓ Absorption
Oral contraceptives	None	None	None	None
Phenytoin	↓ Metabolism	None	None	None
Warfarin	↓ Metabolism	None	None	None
Theophylline	None	↑ Metabolism	None	None

Dosage

- Omeprazole: 20 mg daily for 4–8 weeks
- Lansoprazole: 15–30 mg daily for 4–8 weeks
- Esomeprazole: 20–40 mg daily for 4–8 weeks
- Pantoprazole: 40 mg daily for 4–8 weeks
- Rabeprazole: 20 mg daily for 4–8 weeks
- Ilaprazole: 10 mg daily for 4–8 weeks

Indications

- Reflux oesophagitis and GERD
- Peptic ulcer unresponsive to other medical measures
- As an adjunct to anti-*H. pylori* treatment
- Zollinger–Ellison syndrome

V. Prostaglandin Analogues

- Misoprostol 200 μg four times daily. Useful in preventing NSAID-induced mucosal injury.
- At this dose, it inhibits acid secretion and stimulates bicarbonate and mucus secretion.
- Side effects are diarrhoea, uterine bleeding, uterine contractions and abortifacient activity.

VI. Colloidal Bismuth Compounds

- Bismuth subsalicylate and colloidal bismuth subcitrate.
- Mechanisms of action are two:
    1. These precipitate in acid conditions, binding with proteins in the ulcer base to form a coat that protects against further acid pepsin digestion.
    2. Powerful antimicrobial effect against *H· pylori*.
- Side effects include blackening of tongue, teeth, face, and bismuth toxicity (neurotoxicity).
- At present, bismuth compounds are mostly used as a combination therapy for eradication of *H. pylori*.

VII. Sucralphate (Sucralfate)

- Dose is 2 g BD.
- Forms a protective coating over the ulcers.
- Side effects are reduction in the absorption of warfarin, phenytoin, tetracycline and digoxin.

VIII. Treatment for H. pylori

- Many clinicians administer drugs against *H· pylori* to all patients with peptic ulcer disease, even without documenting the presence of bacteria.
- It reduces the risk of recurrence of ulcer formation.
- Triple or quadruple therapy is recommended.

Treatment of *H. pylori* Infection

- Omeprazole (20 mg BID)# + Clarithromycin (500 mg BID) + Metronidazole (500 mg BID) for 10–14 days
- Omeprazole (20 mg BID)# + Clarithromycin (500 mg BID) + Amoxicillin (1 g BID) for 10–14 days
- Omeprazole (20 mg OD)# + Bismuth subsalicylate (525 mg QID) + Metronidazole (250 mg QID) + Tetracycline (500 mg QID) for 10-14 days

#Lansoprazole (30 mg BID) may be substituted for omeprazole

Long-Term Management

Intermittent Treatment

- For symptomatic relapses less than four times a year
- 4 weeks course of one of the ulcer healing agents

Maintenance Treatment

- Symptomatic relapses more than four times per year.
- History of life-threatening complications like repeated bleeding or perforation.

- Long-term maintenance is with H_2-receptor antagonists (cimetidine 400 mg at night, ranitidine 150 mg at night, famotidine 20 mg at night or nizatidine 150 mg at night).

Surgical Treatment

- For disease refractory to medical therapy, suspicion of malignancy, bleeding ulcer, gastric outlet obstruction, and perforated ulcer,
- For gastric ulcer the procedure of choice is partial gastrectomy with a Billroth I anastomosis.
- Duodenal ulcer treatment could be:
  - Truncal vagotomy plus pyloroplasty or gastroenterostomy
  - Selective vagotomy with pyloroplasty
  - Highly selective vagotomy

Q. Write a short note on dumping syndrome.

- Dumping syndrome refers to symptoms and signs that occur when food reaches the small bowel too rapidly; usually follows surgery for peptic ulcer disease.
- It usually occurs after a sweet food.
- Two phases of dumping may occur: early and late dumping.
- Early dumping syndrome occurs 15–30 minutes after meals and consists of crampy abdominal pain, nausea, diarrhoea, borborygmi, bloating, sweating, tachycardia, palpitations, desire to lie down, light headedness and occasionally syncope. It arises due to rapid emptying of hyperosmolar gastric contents into the small intestine, resulting in fluid shift from blood into the lumen of the gut. This causes intravascular volume contraction and intestinal distension.
- Late dumping occurs 2–3 hours after meals. The patient gets sweating, light headedness, palpitations, tachycardia and occasionally syncope. It is possibly related to excessive insulin secretion causing hypoglycaemia.
- Provocative test for assessing dumping syndrome:
  - A solution of 50–75 g glucose given orally after an overnight fast.
  - Immediately before and up to 180 minutes after ingestion of glucose solution, blood glucose, haematocrit, pulse rate and blood pressure are measured at 30 minutes intervals.
  - Test considered positive, if an early (30 minutes) increase in pulse rate (>10/minutes) or haematocrit >3% occur, or if late (120–180 minutes) hypoglycaemia occurs.
- Treatment:
  - Patient should be asked to avoid simple carbohydrate food and also to take meals in small amounts at frequent intervals with liquids 30 minutes after a meal.
  - Ingesting up to 15 g of guar gum or pectin that increases viscosity of food, thereby slowing down gastric emptying.
  - α-glycosidase inhibitors (e.g. acarbose) for late dumping.
  - Octreotide given subcutaneously before the meal may be used in refractory cases.

Q. Discuss the aetiology, clinical features, salient investigations and management of Zollinger–Ellison syndrome.

- It defines severe peptic ulcer disease secondary to unregulated gastrin release from a non-β cell endocrine tumour (gastrinoma).
- Aetiology
  - More than 80% of gastrinomas are localised in the triangle of the gastrinomas—the convergence of cystic duct, common bile duct, the junction of the second and third portion of duodenum, and the junction of head and body of pancreas.
  - Most gastrinomas arise from the duodenum (about 75%), whereas they are localised in the pancreas in 25% of cases. Other sites include stomach, bones, ovaries, liver and others.
  - Although, more than 60% of these tumours are malignant, they grow slowly in about 70% cases. Metastases occur in local lymph nodes, liver and bones.
  - Besides gastrin, these tumours may secrete pancreatic peptide, somatostatin, adrenocorticotrophic hormone (ACTH) and vasoactive intestinal peptide (VIP).
  - Gastrinoma may be a part of multiple endocrine neoplasia (MEN) type I.
    - An autosomal dominant syndrome
    - Characterised by hyperplasia and/or multiple tumours in the parathyroid, pancreas, duodenum, anterior pituitary, foregut-derived neuroendocrine tissue and adrenocortical glands
- Pathophysiology
  - Excess gastrin stimulates the parietal cells of stomach to produce excess acid.
  - Excess acid leads to severe peptic ulceration.

- Excess acid reaches the upper small intestine, where it reduces the luminal pH to less than 2. At this low pH, pancreatic lipase is inactivated and bile acids are precipitated. This leads to steatorrhoea and diarrhoea.
- Clinical features
  - Most commonly presents between 30 and 50 years of age.
  - Manifestations of peptic ulcerations but of shorter duration. Ulcers are severe, multiple and occur at unusual sites like jejunum or oesophagus.
  - Bleeding and perforation are common. May present as intractable recurrent ulceration, following surgery for peptic ulcer.
  - Diarrhoea occurs in nearly 50% cases.
  - Triad of abdominal pain, weight loss and diarrhoea in the presence of ulcer disease suggests gastrinoma.
  - About one-third of the patients have multiple endocrine neoplasia type I (MEN-I) involving parathyroid, pituitary and pancreas. However, features due to involvement of different organs may span over years.
- Investigations
  - Barium meal shows abnormally coarse gastric mucosal folds and ulcers.
  - Endoscopy reveals multiple ulcers at atypical sites.
  - Fasting gastrin level in blood is markedly raised (other causes of elevated gastrin level include achlorhydria, *H. pylori* infection, pyloric obstruction, renal failure and patients on H_2-blockers or proton-pump inhibitors).
  - Gastric acid analysis—basal acid output (BAO) and maximal acid output (MAO) following pentagastrin administration are elevated (MAO is not done presently).
  - Gastrin provocating tests (secretin stimulation test, calcium infusion test and a standard meal test).
  - Tumour localisation done by ultrasound, endoscopic ultrasound and CT abdomen. The most important study for localisation is somatostatin receptor scintigraphy using ^{111}In-pentetreotide with single-photon emission tomography (SPECT) scanning (ostreoscan).
  - Investigations for MEN-I.
- Treatment
  - Surgical removal of the tumour, whenever possible.
  - Omeprazole can heal the ulcers, but in a higher dose (60 mg/day) and longer duration of treatment. Other proton-pump inhibitors include esomeprazole, pantoprazole, rabeprazole and lansoprazole.
  - Somatostatin and its analogues (octreotide, lanreotide) reduce gastric acid and serum gastrin levels in these patients. They can also reduce progression of tumour in some patients.
  - Unresponsive patients are treated by total gastrectomy.

Q. Briefly discuss the causes and differential diagnosis of dyspepsia.

- Dyspepsia is a collective description of a variety of gastrointestinal symptoms.

• Upper abdominal pain, related or unrelated to food	• Early repletion or satiety after meals
• Gastro-oesophageal reflux and heartburn	• Feeling of abdominal distension or bloating
• Anorexia, nausea and vomiting	• Flatulence (burping, belching) and aerography

- Organic dyspepsia means clinical and laboratory investigation indicate an underlying organic disease that is likely to be the cause of the symptoms. Ulcer dyspepsia is one form of organic dyspepsia where dyspeptic symptoms are associated with peptic ulcer.
- Non-ulcer dyspepsia (functional dyspepsia) is dyspepsia for which no cause can be found.
- Flatulent dyspepsia is usually occurs due to a functional disorder, where dyspeptic symptoms like early satiety, flatulence, bloating and belching predominate.

Causes

• Functional dyspepsia	• Drugs
• Dyspepsia associated with organic diseases of upper gastrointestinal tract	• Alcohol
• Peptic ulcer	• Pregnancy
• Peptic oesophagitis and gastroesophageal reflux disease (GERD)	• Depression
• Gastric carcinoma	• Anxiety neurosis
• Lactose intolerance	
• Dyspepsia associated with other conditions	
• Pancreatic diseases	
• Crohn's disease	
• Colon malignancy	
• Cardiac, renal, hepatic failure	
• Carcinoma lung	

Common Drugs Causing Dyspepsia

• Acarbose	• Metformin
• Bisphosphonates (e.g. alendronate)	• Miglitol
• Antibiotics (e.g. erythromycin)	• Non-steroidal anti-inflammatory drugs
• Codeine	• Orlistat
• Corticosteroids	• Theophylline
• Iron	

Differential Diagnosis

- GERD
  - Predominant heartburn, heartburn relieved by an antacid and heartburn exacerbated by stooping or lying flat.
  - Regurgitation.
- Peptic ulcer disease
  - Predominant epigastric pain or discomfort.
  - Periodic symptoms (present for some months of the year and absent for other months).
  - Pain or discomfort relieved with food or causes nocturnal waking.
- Gastric malignancy
  - Progressive dysphagia, weight loss, gastrointestinal bleeding, anaemia or persistent vomiting.
  - A history of pernicious anaemia or partial gastrectomy (increased incidence of gastric malignancy).

Q. Discuss the aetiology, clinical features, investigations and management of non-ulcer dyspepsia (functional dyspepsia; nervous dyspepsia; non-organic dyspepsia).

Aetiology

- Even on detailed investigation, no cause can be found.
- Symptoms are believed to be generated by disturbances in the motor function of the gastrointestinal tract.
- The motor dysfunction is analogous that occurring in the irritable bowel syndrome (refer elsewhere), and indeed both irritable bowel syndrome and non-ulcer dyspepsia often exist together in the same individual.
- *H. pylori* may be responsible in some cases.
- Besides psychological factors, neurological and gut peptide factors are also implicated in the genesis.

Clinical Features

- Usually in young females (less than 40 years of age)
- All the dyspeptic symptoms are present in varying degrees
- Abdominal pain, nausea and bloating after meals
- Pain and nausea on waking in the morning is characteristic
- Symptoms of irritable bowel syndrome such as pellet-like stools and feeling of incomplete evacuation after defaecation
- History of stress like worries, concern about finance, employment and family affairs
- Examination reveals inappropriate abdominal tenderness
- All the organic causes of dyspepsia like drug intake, depression, pregnancy, alcohol abuse, etc. have to be excluded before making a diagnosis of non-ulcer dyspepsia
- Alarming features that merit thorough investigations include weight loss, anorexia, dysphagia and haematemesis or melaena.

Investigations

- Blood count, ESR and occult blood in stools to exclude organic disorders
- Liver function tests to exclude alcoholism
- Pregnancy tests to exclude pregnancy
- Barium meal to exclude organic diseases
- Endoscopy to exclude organic diseases. Required before a trial of H_2-blockers or proton-pump inhibitors in presence of any of the following:
  - Age >55 years
  - Dysphagia
  - Protracted vomiting
  - Anorexia or unexplained weight loss

- • Melaena
- • Anaemia
- • Palpable mass
- • Previous peptic ulcer disease
- • Jaundice
- • Family history of gastric malignancy
- Non-invasive tests for *H. pylori*, if above-mentioned risk factors are absent.

Diagnostic Criteria

Rome III Criteria for Functional Dyspepsia

A. At least 3 months, with onset at least 6 months previously, of one or more of the following four:
   1. Bothersome postprandial fullness
   2. Early satiation
   3. Epigastric pain
   4. Epigastric burning
   AND
 B. No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms

- Rome III criteria divide functional dyspepsia into two types: Epigastric pain syndrome (EPS) and post-prandial distress syndrome (PDS). Any one of first two criteria is for EPS while any one of last two criteria is for PDS.
- A diagnosis of functional dyspepsia can only be established after exclusion of other causes of dyspepsia.

Management

- Proper explanation and reassurance.
- Stress factors tackled by counselling.
- Avoid cigarette smoking and alcohol abuse.
- If endoscopy is non-contributory, initiate empirical treatment.
  - • Metoclopramide 10 mg TID or domperidone 10–20 mg TID before meals for nausea, vomiting and bloating.
  - • Mosapride, itopride or levosulpiride may also be tried.
  - • H_2-receptor antagonists or proton-pump inhibitors for 4-6 weeks, if pain is a predominant symptom.
  - • *H. pylori* eradication if test is positive; may provide small degree of benefit.
  - • Selective serotonin reuptake inhibitors may be effective in some patients.

Distinguishing Features

Non-ulcer dyspepsia	Ulcer dyspepsia
• Pain not episodic	• Pain episodic (periodicity)
• Pain present throughout the day	• Pain occurs only on empty stomach
• Unaffected by antacids	• Relieved by antacids
• Pain provoked by food	• Pain relieved by food
• Diffuse abdominal pain referred to more than one site	• Localised abdominal pain referred to epigastrium
• Pain at night, waking the patient from sleep is rare	• Pain at night, waking the patient from sleep is common
• Pain not relieved by vomiting and patient cannot eat afterwards	• Pain relieved by vomiting and patient can eat immediately

Q. Discuss the classification, aetiology, clinical features, investigations and management of malabsorption syndrome.

- The term 'maldigestion' indicates impaired breakdown of nutrients (carbohydrates, proteins, and fats) to absorbable split-products (mono-, di-, or oligosaccharides, amino acids, oligopeptides, fatty acids, monoglycerides). On the other hand, the term malabsorption strictly means defective mucosal uptake and transport of adequately digested nutrients including vitamins and trace elements.
- However, in practice, malabsorption is defined as impairment of digestion and/or absorption from gastrointestinal tract.

Classification and Aetiology

Disorders of intraluminal digestion

A. Defect in substrate hydrolysis
- Enzyme deficiency
  - Chronic pancreatitis
  - Cystic fibrosis
  - Pancreatic carcinoma

- Enzyme inactivation
- Rapid transit of food through gut
  - Zollinger–Ellison syndrome
  - Gastroenterostomy
  - Partial gastrectomy

B. Defect in fat solublisation
- Reduced bile salt synthesis
- Reduced bile secretion
- Bile salt deconjugation and precipitation in gut
  - Parenchymal liver diseases
  - Cholestatic jaundice
  - Zollinger–Ellison syndrome
  - Stagnant loop syndrome or blind loop syndrome (colonisation of small bowel by bacteria)

- Increased bile salt loss in faeces
  - Terminal ileal disease (e.g. Crohn's disease, tuberculosis)
  - Terminal ileal resection

C. Defect in luminal availability of factors
- Lack of intrinsic factor
- Increased vitamin B_{12} consumption in gut
  - Pernicious anaemia
  - Stagnant loop or blind loop syndrome

Disorders of transport in the intestinal mucosal cell

A. Defect in brush-border hydrolysis (mucosa normal histologically)
  - Lactase deficiency

B. Defect in epithelial transport (mucosa often abnormal histologically)
  - Coeliac disease
  - Tropical sprue
  - Lymphoma
  - Whipple's disease
  - Giardiasis
  - Radiation enteritis
  - AIDS

Disorders of transport from mucosal cell

A. Lymphatic obstruction
  - Abdominal lymphoma
  - Tuberculosis
  - Lymphangiectasia
B. Defect in epithelial processing
  - Abetalipoproteinaemia

Drugs and systemic diseases causing malabsorption (see the following boxes)

Drugs Causing Malabsorption

Drug	Mechanisms
Colchicine	Inhibits crypt cell division and lactase
Neomycin	Precipitation of bile salts in gut; inhibition of lactase
Methotrexate	Folic acid antagonist causing inhibition of crypt cell division
Cholestyramine	Binding bile salts
Laxatives	Multiple mechanisms

Systemic Diseases Associated with Malabsorption

Disease	Mechanisms
• Addison's disease	Not clear
• Thyrotoxicosis	Rapid transit through gut
• Hypothyroidism	Villous atrophy; pancreatic insufficiency
• Diabetes mellitus	Autonomic insufficiency; bacterial overgrowth; pancreatic insufficiency (causing diabetes)
• Collagen vascular diseases	Villous atrophy; bacterial overgrowth; amyloidosis

Clinical Features

- Insidious onset and gradual progression
- General features
  - Include diarrhoea, abdominal pain, distension, loss of weight, anaemia and vague ill health
- Specific features
  - Due to defective absorption of different constituents

• **Protein**	Progressive emaciation, pitting pedal oedema
• **Fat**	Loss of weight, diarrhoea, loose, pale, bulky offensive stool that float on water and are difficult to flush away (steatorrhoea)
• **Carbohydrate**	Abdominal distension, belching, bloating feeling in abdomen
• **Vitamins**	
• Vitamin A	Follicular keratosis, night blindness, xerophthalmia, keratomalacia
• Vitamin D	Muscular irritability, tetany, features of osteomalacia
• Vitamin K	Haemorrhagic tendencies
• Vitamin B_1 and B_2	Angular stomatitis, cheilosis, glossitis, neuropathy
• Folic acid	Macrocytic anaemia, glossitis
• **Minerals and electrolytes**	
• Sodium	Muscle cramps, weakness, hypotension
• Potassium	Weakness, areflexia, intestinal distension, cardiac arrhythmias
• Calcium	Muscular irritability, tetany, features of rickets, features of osteomalacia
• Magnesium	Weakness, tingling sensation, tetany
• Zinc	Anorexia, weakness, tingling, impaired taste
• Iron	Hypochromic microcytic anaemia, glossitis, koilonychia
• Water	Dehydration, low blood volume

- Bile acid malabsorption.
  - Failure of absorption of bile acids (e.g. chenodeoxycholic and deoxycholic acids) by distal ileum results in spillover of bile acids into colon, where they induce secretion of sodium and water, producing loose and watery stools.

Investigations

- Barium meal follows through
  - Shows non-specific features such as dilated loops with flocculation and segmentation of barium.
  - Specific structural abnormalities in Crohn's disease, diverticula and strictures.
- Tests for fat absorption
  - Sudan III staining of stool for fat globules.
  - Stool fat excretion in 1 day is more than 7 g (normal is less than 7 g/day on a 100 g/day of fat diet). Generally, stools are collected over a period of 72 hours. It does not differentiate between small intestinal, hepatobiliary and pancreatic causes.
  - Measurement of fat-soluble vitamins (A, D, E, K) levels in the blood; prothrombin time.
  - Plasma vitamin A level after 2–3 days of oral retinol will be lower than normal.
  - Near-infrared reflectance analysis
  - ^{14}C-triolein breath test involves measurement of breath carbon dioxide after ingestion of radiolabeled triglyceride triolein.
- Tests for carbohydrate absorption
  - Glucose tolerance test shows absence of rise in blood glucose levels.
  - Low blood sugar level.

- D-xylose absorption test measures urinary excretion of D-xylose over 5 hours after ingestion of a 25 g oral dose; less than 4 g is abnormal. It indicates enteric malabsorption instead of pancreatic cause.
- LTT (lactose tolerance test) is abnormal—after 50 g lactose is given orally, blood samples are taken every 20 minutes for 2 hours. Normally, blood glucose shows a rise of more than 20 mg/dL.
- Hydrogen breath test to diagnose lactase deficiency—50 g lactose is given orally and breath hydrogen measured every hour for 4 hours. Normal value is less than 10 ppm increase above baseline.
- Tests for protein absorption
  - Serum albumin level will be low.
  - Measurement of nitrogen in the 24-hour stool will be more than 2.5 g.
  - Labelling serum proteins with radioactive chromium and measuring radioactivity in stool is a test for protein-losing enteropathy.
  - α_1-antitrypsin content in a 3 days collection of stools (normally no antitrypsin in stool).
- Test for bile acid malabsorption.
  - Selenium homocholic acid taurine (SeHCAT) test in which, Se-labelled bile acid is administered orally and total body retention is measured with a gamma camera after 7 days. Retention value of less than 10% is considered abnormal.
- Tests for absorption of other substances
  - Serum B_{12} level will be low
  - Schilling test for absorption of B_{12} (described elsewhere)
  - Serum levels of iron, folate and calcium will be low
  - Macrocytic anaemia in B_{12} and folic acid deficiency
  - Prolonged prothrombin time
  - Low serum sodium and potassium
  - Low serum magnesium and zinc levels
- Breath tests
  - Cholyl-^{14}C-glycine for bacterial overgrowth
  - Lactose H_2 for lactose intolerance (e.g. in bacterial overgrowth)
- Wireless capsule endoscopy
  - Allows for visualisation of entire small bowel and allows for much more detailed evaluation of small bowel mucosal disease than barium studies.
- Small intestinal biopsy (duodenal or jejunal)

Treatment

- Gluten-free diet in coeliac disease
- Pancreatic supplements in pancreatic insufficiency
- Low-fat diet and cholestyramine for bile acid deficiency
- Replacement therapy for anaemia, bone disease and coagulation defects
- Oral folic acid, oral iron and intramuscular B_{12}
- Vitamin D and calcium supplements
- Vitamin B complex
- Cholestryramine (bile acid binder) for bile acid malabsorption
- Treat dehydration and electrolyte deficiency by intravenous infusion

Q. Discuss the aetiology, pathology, clinical features, complications, investigations and treatment of coeliac disease (non tropical sprue; gluten-induced enteropathy).

Definition

- A chronic intestinal disease-producing malabsorption and caused by intolerance to gluten.
- Characterised by immune-mediated enteropathy (villous flattening) resulting in maldigestion and malabsorption.
- Clinical and histological improvement after withdrawal of dietary gluten.

Aetiology

- Immunological damage of the mucosa due to gluten protein of wheat. Gluten is also present in barley and rye. The toxic component in gluten is gliadin.
- High association with HLA DQ2 and DQ8.

Pathophysiology

- Gluten is the water-insoluble seed storage protein in wheat, rye and barley. Gliadin is the alcohol-soluble component of gluten.
- α-gliadin and other related peptides bind with tissue transglutaminase in enterocytes.

- α-gliadin is rich in glutamine; transglutaminase deaminates glutamine residues, forming glutamic acid. Deamidation enhances the immunogenicity of α-gliadin.
- These altered gliadin peptides are then presented to local intestinal T cells and recognised as foreign, thereby stimulating an immune response.
- Subsequently, CD4 + T lymphocytes infiltrate in lamina propria and CD8+ in intestinal epithelium.
- Recognition of HLA-bound gluten peptides by T cells, leads to their activation and clonal expansion of B cells that produce antibodies.
- Antibodies produced by plasma cells are directed against a variety of antigens including transglutaminase, endomysium, gliadin and reticulin. This leads to intense local inflammatory reaction in the intestines producing villous-fattening. This in turn leads to malabsorption.

Pathology

- Mucosa of duodenojejunal flexure shows the abnormalities
- Characteristic features are partial villous atrophy or subtotal villous atrophy
- Lamina propria demonstrates cellular infiltrates consisting of plasma cells and lymphocytes

Clinical Features

- Seen in both children and adults, but more common in children.
- Diagnosed typically in early childhood around the age of 2 years. A second peak is found around the age of 40 years.
- Features in adults.
  - Range from mild anaemia to florid malabsorptive state
  - The most common cause of anaemia is iron deficiency; less commonly, it is due to folate and/or vitamin B_{12} deficiency
  - Diarrhoea and weight loss
  - Peripheral neuropathy (B_1 and B_{12} deficiency), hypoproteinaemia, oedema, bone pain and tetany
  - Vitamin deficiency features
  - Clubbing (20%), glossitis, angular stomatitis and skin pigmentation
  - Amenorrhoea and infertility
  - Fingerprint show epidermal ridge atrophy in 90%
  - A number of other autoimmune syndromes have been associated with coeliac disease. These include type 1 diabetes, autoimmune thyroid disease, rheumatoid arthritis, systemic lupus erythematosus, Addison's disease and others.
  - Other uncommon extraintestinal features include idiopathic pulmonary haemosiderosis, IgA nephropathy, elevated liver enzymes and liver failure, myocarditis and arthritis

Complications

- Dermatitis herpetiformis:
  - Chronic pruritic disease characterised by presence of intensely pruritic, symmetrical papul-vesicular rash that evolves to crusting lesions broadly distributed over the body, but especially on the forearms, knees, buttocks, wrists and scalp.
  - Mucous membranes are uncommonly involved.
  - On biopsy, papillary dermal neutrophilic microabscesses are characteristically seen.
  - On direct immunofluorescence, granular deposition of immunoglobulin A is detected.
  - Direct immunofluorescence confirms the diagnosis.
  - Also have IgA antibodies directed against epidermal transglutaminase, which is homologous to tissue transglutaminase antibody.
  - Gluten-free diet is the treatment of choice.
  - If not responsive, dapsone may be tried.
- Malignancies particularly intestinal lymphoma are mainly involving jejunum
- Gastrointestinal malignancies
- Pneumococcal infections
- Peripheral neuropathy, epilepsy and ataxia
- Osteomalacia
- Amyloidosis
- Microscopic colitis

Investigations

- Serologic tests
  - IgA anti-endomysial antibodies (EMA; 85–100% sensitive and 95–100% specific)
  - IgA antitissue transglutaminase (tTG) antibodies

- IgG and IgA antigliadin antibodies (not routinely recommended for diagnosing coeliac disease)
- IgG deamidated gliadin peptide antibodies better than antigliadin antibodies
- IgG-based tests are useful for detecting coeliac disease in IgA-deficient patients.
- Patients should not restrict their diet before testing for antibodies.
- Abnormal jejunal biopsy
  - A biopsy may be omitted if patient has high antibody titres (tTG >10x normal and positive EMA), and an appropriate HLA type.
- Tests indicating malabsorption of proteins, carbohydrate, fat and vitamins

Serologic Tests for Coeliac Disease

Assay	Sensitivity (%)	Specificity (%)
IgA antiendomysial antibody	85–98	96–100
IgA antitissue transglutaminase antibody	90–98	94–97
IgA antigliadin antibody	80–90	85–95
IgG antigliadin antibody	75–85	75–90

Treatment

- Strict gluten-free diet, indefinitely. Avoid wheat and wheat products, rye and barley.
- Rice, corn, soybean, potato, nuts and beans, meat and fruit are safe. Pure oat in moderate quantities is also safe.
- Beer must be completely avoided, even from alcohol-free brands, as its manufacture involves the fermentation of various gluten-containing cereals. The same is true for all kinds of whisky, obtained from malt distillation procedures.
- Corticosteroids are required rarely. Useful in critically ill patients who present with acute cliac crisis manifested by severe diarrhoea, dehydration, weight loss, acidosis, hypocalcaemia and hypoproteinaemia. Also required for the rare patients who present with gliadin shock after a gluten challenge.
- Vitamin and mineral supplementation including iron administration.
- Dairy products are avoided in beginning as secondary lactase deficiency is often associated with coeliac disease.

Q. Discuss the aetiology, pathology, clinical features, investigations and treatment of tropical sprue (idiopathic tropical malabsorption syndrome).

Definition

- Malabsorption occurring in patients of tropics in the absence of other intestinal diseases or parasites.

Aetiology

- It is unknown, but some infective organism is suspected as antibiotics are very useful in the treatment of this disease.
- Some of the implicated bacteria include *E. coli*, *Klebsiella* and *Enterobacter*.
- Folic acid deficiency is another postulation.

Pathology

- Jejunal biopsy shows partial villous atrophy.
- A normal jejunal biopsy rules out tropical sprue, but an abnormal biopsy does not diagnose it since similar abnormalities are seen in some normal tropical subjects, and also in some other conditions.

Clinical Features

- Three phases:
  - Initial phase of active diarrhoea (common in India)
  - Intermediate phase
  - Last phase (frank malabsorption)
- Spontaneous remissions and relapses may occur
- Diarrhoea, abdominal distension, anorexia, weight loss and fatigue
- Megaloblastic anaemia, oedema, glossitis and stomatitis

Investigations

- Stool examination to exclude *Giardia*, *Entamoeba histolytica*, *Yersinia*, *Cryptosporidium* and other pathogens
- Megaloblastic anaemia

- Hypoalbuminaemia
- Abnormal tests for fat absorption
- D-xylose test abnormal
- Vitamin B$_{12}$ malabsorption
- Tissue transglutaminase and endomysial antibodies negative
- Partial villous atrophy on jejunal biopsy

Treatment

- Tetracycline or oxytetracycline 1 g daily in four divided doses for 6 months
- Folic acid 5 mg daily (along with tetracycline)
- Correction of deficiencies of fluids, electrolytes, vitamins and iron
- Symptomatic treatment for diarrhoea

Q. Discuss the aetiology, clinical features, investigations and management of lactose intolerance.

Aetiology

- The term lactose intolerance indicates that lactose malabsorption causes gastrointestinal symptoms. It occurs due to deficiency of lactase, an enzyme occurring in the brush border membrane of the intestinal mucosa that hydrolyses lactose to its components galactose and glucose.
- Lactose (primary carbohydrate in milk) cannot be hydrolysed, and hence, it goes to colon where it is fermented by bacteria to produce methane, hydrogen and carbon dioxide, which can lead to gastrointestinal symptoms.
- Primary lactase deficiency is inherited and characterised by normal intestinal biopsy. Lactase activity begins to decrease after weaning, usually after 2 years of age.
- Secondary lactase deficiency can be the consequence of any condition that damages the small intestinal mucosa brush border or significantly increases the gastrointestinal transit time. It is often associated with abnormal intestinal biopsy. Seen in coeliac disease, tropical sprue, Crohn's disease, giardiasis and viral gastroenteritis.
- Congenital lactase deficiency is very rare.

Clinical Features

- Low lactase levels per se do not result in symptoms. Whether and to what extent symptoms occur depend on several factors such as amount of lactose consumed, individual sensitivity, and rate of gastric emptying.
- Abdominal colic, abdominal distension, increased flatus and diarrhoea after ingesting milk or milk products
- Headache, lightheadedness, loss of concentration, fatigue, cardiac dysrhythmias and mouth ulcers may be associated with lactose malabsorption.
- Improvement of symptoms on withdrawal of milk or milk products

Investigations

- Hydrogen breath test
  - Undigested lactose is fermented by the colonic microflora with production of hydrogen detectable in expired air.
- Measurement of lactase activity in a jejunal biopsy specimen

Treatment

- Lactose-free or lactose restricted diet (avoidance of milk and dairy products). However, it may produce serious nutritional deficiencies, particularly calcium deficiency. Most people with lactose intolerance can tolerate some amount of lactose in their diet.
- Gradually introducing small amounts of milk or milk products may help some people adapt to them with fewer symptoms. Often, people can better tolerate milk or milk products by taking them with meals.
- Exogenous β-galactosidase
  - Enzyme replacement therapy with microbial exogenous lactase (obtained from yeasts or fungi) seems to be effective without any significant side effects.
  - Enzymes are added in a liquid form to milk before its consumption or administered in a solid form (capsules or tablets) together with milk and dairy products.
- Other therapeutic modalities include use of yoghurt and probiotics as source of β-galactosidase. Yoghurt delays gastric emptying and intestinal transit causing slower delivery of lactose to the intestine, thus optimising the action of residual β-galactosidase in the small bowel and decreasing the osmotic load of lactose. It also contains microorganisms that produce lactase.

Q. Give a brief account of Whipple's disease.

- It is a chronic multisystem disease associated with malabsorption.
- It is caused by gram-positive bacteria, *Tropheryma whippelii*.
- There are characteristic PAS positive macrophages in the small intestine and other involved organs (including joints, lungs, central nervous system, heart and eyes). These macrophages cause lymphatic blockade in the lamina propria of small intestine causing malabsorption.

Clinical Features

- Eight times more common in males than in females.
- Symptoms are diarrhoea, chronic, migratory, non-destructive polyarthritis, weight loss and abdominal pain. Steatorrhoea is uncommon.
- Other features include migratory arthralgias, fever, ophthalmologic features and neurologic features (dementia, nystagmus, myoclonus and ophthalmoplegia in late stages).
- Signs include generalised lymphadenopathy, arthropathy, skin pigmentation, abdominal distension and tenderness.
- Cardiac involvement leads to mitral and aortic regurgitation.

Investigations

- Elevated erythrocyte sedimentation rate and C-reactive protein.
- Tests for malabsorption.
- Negative rheumatoid factor.
- Jejunal biopsy and biopsy of other involved tissues show plenty of PAS positive macrophages that contain small bacilli.
- PCR tests for *T. whipplii* in saliva, stool or joint fluid.

Treatment

- Trimethoprim–sulphamethoxazole (double strength tablet) should be given twice a day for 1 year. Oral treatment should be preceded by a 2-week course of parenteral therapy with ceftriaxone (2 g daily) or by meropenem.

Q. Briefly discuss the aetiology, clinical features, investigations and treatment of giardiasis.

Aetiology

- Organism is *Giardia lamblia*.
- Infection occurs by ingestion of cysts through contaminated water or by faecal--oral route.
- Trophozoites attach to the mucosa of duodenum and jejunum, causing alteration in small bowel functions. Most often, there is no local destruction or invasion.
- Malabsorption that occurs in many patients is due to loss of brush border enzyme activities, while in some cases there is flattening of villi.
- Patients with hypogammaglobulinaemia suffer from prolonged and severe infection that may be unresponsive to standard treatment.

Clinical Features

- Incubation period is 1–3 weeks (median 7–10 days).
- Starts as diarrhoea, nausea, vomiting, anorexia, weakness and abdominal pain. Fever and blood in stool are rare.
- Symptoms may persist from a few days to weeks or months to years.
- Secondary lactase deficiency is common.
- Many patients are asymptomatic.
- Individuals with chronic giardiasis may present with or without having experienced antecedent acute symptoms.
- Diarrhoea may not be a prominent symptom in these patients who often have increased flatus, loose stools, malabsorption, weight loss and growth retardation.

Investigations

- Repeated examination of stool for cysts.
- Detection of giardia antigen in stool using immunoassays.
- Duodenal or jejunal fluid microscopy will demonstrate the organism.
- Jejunal biopsy shows the giardia on the mucosa.
- Long-standing cases show steatorrhoea, malabsorption of xylose, vitamin B_{12} and lactose intolerance.

Treatment

- Tinidazole 40 mg/kg as a single dose, repeated after 1 week.
- Metronidazole 2 g daily for 3 days or metronidazole 200 mg thrice daily for 7 days.
- Ornidazole 500 mg twice a day for 2–3 days
- Nitazoxanide 500 mg twice a day for 3 days.
- Metronidazole 800 mg TID for 3 weeks in refractory cases.
- Albendazole 400 mg once a day for 5–10 days
- Avoid lactose-containing foods for at least one month after therapy.

Q. What is Traveller's diarrhoea? Briefly explain.

- Food and water contaminated with faecal matter are the main reservoirs for the pathogens that cause traveller's diarrhoea.

Aetiology

• *E. coli* (toxigenic and enteroaggregative)	• *Giardia lamblia*
• *Vibrio parahaemolyticus*	• *Entamoeba histolytica*
• *Vibrio cholerae* — El tor biotype	• Rota virus
• *Shigella*	• Norwalk virus
• *Salmonella* (nontyphoid)	
• *Campylobacter*	
• Commonly, no organism is identified	

Clinical Features

- Usually affects intercontinental travellers.
- Abrupt onset, watery diarrhoea, lasting 2–5 days
- Abdominal cramps, nausea, vomiting, anorexia and fever
- Diffuse tenderness over abdomen

Treatment

- Usually self-limited and no treatment is required.
- Correction of dehydration by oral rehydration supplements.
- Antidiarrhoeal agents and antibiotics are required rarely. If patient has fever or has bloody diarrhoea, norfloxacin or ciprofloxacin may be used. Azithromycin is used if patient is allergic to quinolones or is pregnant.
- Trimethoprim–sulphamethoxazole and doxycycline are no longer recommended because of the development of wide-spread resistance.
- Rifaximin, a poorly absorbed rifampicin derivative, is highly effective against non-invasive bacterial pathogens.
- Loperamide may be used along with an antibiotic to reduce symptoms.

Prevention

- Doxycycline 100 mg/day for a few weeks.
- Bismuth subsalicylate is given 60 mL four times a day. Avoid if allergic to aspirin, pregnant or on anticoagulants. Also avoid if taking doxycycline (e.g. for malaria prophylaxis).
- Norfloxacin or ciprofloxacin or rifaximin once a day.
- Probiotics may be useful.

Q. Briefly describe carcinoid tumours and carcinoid syndrome.

- Carcinoid tumours are neoplasms of neuroendocrine cells (e.g. enterochromaffin cells). These are now categorised as neuroendocrine tumours (NET).
- Classified on the basis of their embryologic origin:
  - Foregut (lungs, bronchi and stomach)
  - Midgut (small intestine, appendix and proximal large bowel)
  - Hindgut (distal large bowel, rectum).
- Common sites of NET in the gastrointestinal tract are ileum, appendix and rectum.
- Carcinoid syndrome refers to the systemic symptoms produced, when the secretory products of these tumours are released into the systemic circulation.

- This syndrome usually occurs after hepatic metastasis of midgut carcinoids as normally liver is able to deactivate these secretory products.
- In contrast, patients with foregut (bronchial and extraintestinal) carcinoids can present with carcinoid syndrome without hepatic metastases, since their secretory products normally bypass liver and enter systemic circulation directly.
- Hindgut tumours seldom produce this syndrome since they do not secrete these products.
- Intestinal carcinoids show a high tendency for hepatic metastases.

Secretory products	
• Serotonin	• Bradykinins
• Histamine	• Adrenocorticotrophic hormone
• Tachykinins	• Corticotrophin releasing factor
• Motilin	• Prostaglandins

Clinical Features

- Cutaneous flushing involving head and neck (blush area) associated with lacrimation, periorbital oedema, tachycardia and hypotension. This may last for a few minutes to hours. Flushing may be precipitated by cheese, nuts and wine.
- Diarrhoea with borborygmic cramps and malabsorption. Flushing and diarrhoea are precipitated by food, alcohol or exercise.
- Facial telangiectasia is purple telangiectasia, most marked over malar area.
- Right heart valve lesions, especially tricuspid regurgitation and pulmonary stenosis.
- Wheeze occurs, due to bronchoconstriction.
- Pellagra-like lesions are due to conversion of tryptophan to serotonin (normally, niacin is produced from tryptophan).
- General features include hepatomegaly, due to hepatic metastases, intestinal obstruction and bleeding, and a tumour-associated myasthenia.

Diagnosis

- Increased urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA) in 24 hour collection (more than 9 mg).
- Elevated plasma levels of chromogranin A.
- Serotonin level in blood and platelets is high.
- CT, MRI and somatostatin receptor scintigraphy, positron emission tomography (PET) with radiolabeled 5-hydroxy-tryptophan, and occasionally laparotomy for localisation.
- Measurement of increased concentration of serotonin in tumour tissue.

Treatment

- Avoidance of conditions and diets precipitating flushing and diarrhoea
- Supplementation of food with niacin
- Bronchodilators for wheeze
- Loperamide for diarrhoea
- Serotonin receptor antagonists (cyproheptadine, methysergide and ondansetron) to control diarrhoea. These agents may also control flushing in some cases
- Analogues of somatostatin (e.g. octreotide and lanreotide) are useful to control flushing
- Surgical resection of the tumour
- Excision of hepatic metastases or hepatic artery embolisation with or without chemotherapy

Q. Discuss the aetiology, clinical features, investigations and management of ischaemic colitis.

Blood Supply

- Superior mesenteric artery supplies proximal two-thirds of transverse colon, ascending colon, and caecum.
- Inferior mesenteric artery supplies distal transverse colon, descending colon, sigmoid colon, and proximal aspect of rectum.
- Internal iliac artery supplies mid and distal rectum via rectal arteries.
- Marginal artery of Drummond extends along the periphery of colonic mesentery, giving rise to vasa recta and linking inferior mesenteric artery to superior mesenteric artery. Collateral vessels help to ensure adequate perfusion, if one of the main branches become occluded.
- Splenic flexure (Griffiths point) and sigmoid colon (Sudeck point) are the most sensitive areas to decreased blood flow. These "watershed" areas are where circulation from superior mesenteric artery and inferior mesenteric artery met, and where inferior mesenteric artery and rectal arteries meet. These areas rely on marginal artery of Drummond to provide collateral flow.
- Thus, left colon and splenic flexure involved in 75% of ischaemic colitis.

- Severity of ischemia will determine, whether transmural necrosis (gangrenous colitis) occurs or only mucosa and/or submucosa is involved (nongangrenous colitis).

Aetiology

- Systemic hypoperfusion.
- Occlusion of the inferior mesenteric artery leading to ischemia of left colon (thrombosis and embolism).
- Occasionally, it can develop due to vasculitis or ingestion of oral contraceptives.
- Drugs (e.g. alosetron, antihypertensive drugs, digoxin, cocaine, etc.).
- Sickle cell disease.
- Irritable bowel syndrome and COPD (2-4 times more prone to develop ischaemic colitis).

Clinical Features

- Most patients are above 60 years of age.
- Colicky lower abdominal pain (often associated with urge to defaecate), nausea and vomiting.
- Diarrhoea with blood and mucus.
- Tenderness and guarding over left lower abdomen, especially left iliac fossa.
- Persistent bleeding and pain suggest stricture formation.
- A few patients may progress to shock with generalised abdominal pain, indicating peritonitis secondary to gangrene.
- Needs to be differentiated from acute mesenteric ischemia (most patients with mesenteric ischemia present with sudden onset of severe abdominal pain out of proportion to tenderness; they appear profoundly ill and they do not have bloody stools until the late stages).

Investigations

- Leucocytosis.
- Plain radiograph of abdomen shows thumb printing at splenic flexure and descending colon.
- Double contrast barium enema demonstrates involvement of splenic flexure and descending colon. Mucosal abnormalities are thumb printing and ulceration.
- CT abdomen.
- Colonoscopy has replaced barium studies as it is more sensitive. Sigmoidoscopy shows normal rectal mucosa and bleeding descending from above.
- Arteriography confirms the diagnosis in patients with obstructive lesions.

Treatment

- Conservative management with intravenous fluids, haemodynamic stabilisation, discontinuation or avoidance of vasoconstrictive agents, bowel rest and empiric antibiotics.
- Surgical treatment for peritonitis and strictures.

Q. What are the causes of lower gastrointestinal bleeding?

- Lower gastrointestinal tract extends from below the ligament of Treitz.

Causes

• Haemorrhoids, polyps	• Ulcerative colitis
• Carcinoma colon and rectum	• Ischaemic colitis
• Diverticular disease	• AV malformations
• Angiodysplasia	• Meckel's diverticulum

Q. Discuss the aetiology, clinical features, investigations and treatment of pseudomembranous colitis (antibiotic–associated colitis).

Aetiology

- Diarrhoea occurs due to a toxin produced by *Clostridium difficile*, when the normal bacterial flora is altered or suppressed by antibiotics.
- Commonly implicated antibiotics are:
  - Tetracycline
  - Ampicillin

- Lincomycin
- Clindamycin
- Others—diphenoxylate, quinolones, other antibiotics
- Other risk factors include prolonged hospital stay and elderly patients.

Pathogenesis

- Two prerequisites for developing *C. difficile* associated diarrhoea:
  - Disruption of normal gastrointestinal flora causing diminished colonisation resistance favouring *C. difficile*.
  - Acquisition of *C. difficile* from an exogenous source.
- Two toxins required to cause diarrhoea:
  - Toxin A disrupts colonic mucosal cell adherence to colonic basement membrane and damages villous tips.
  - Toxin B enters the cell by endocytosis and induces apoptosis.
- Both toxins stimulate monocytes and macrophages, which in turn release interleukin 8, resulting in tissue infiltration with neutrophils.
- Extent of clinical manifestations depends on the immune response to *C. difficile*. Patients with low antitoxin A IgG levels manifest more severe disease unlike those with higher levels who usually recover spontaneously.

Pathology

- Rectum and colon show a yellowish membrane adherent to the eroded mucosa (pseudomembrane).
- Membrane is made up of fibrin and polymorphs.

Clinical Features

- It usually occurs in adults.
- Patient is usually on antibiotics or would have received antibiotics within last 8 weeks.
- Profuse watery diarrhoea with abdominal cramps.
- Blood in the stools may occur.
- Complications include dehydration, electrolyte disturbances, hypoalbuminaemia, toxic megacolon, bowel perforation, hypotension, renal failure, sepsis and death. Diarrhoea may be absent, if patient develops paralytic ileus or fulminant colitis

Investigations

- Sigmoidoscopy or colonoscopy shows yellowish membrane (pseudomembrane).
- Histologic features of pseudomembrane (refer pathology).
- Stool contains toxin produced by *C. difficile* (should be done only on diarrhoeal stools unless paralytic ileus is suspected).
- Glutamate dehydrogenase detection in stool by enzyme immunoassay (present in both toxigenic and non-toxigenic strains of *C. difficile*). Helpful in ruling out disease.
- Stool culture.
- Nucleic acid amplification tests (e.g. PCR) for detecting genes of toxin A and B.

Treatment

- Withdraw the offending drug.
- Oral or intravenous rehydration.
- Oral metronidazole 500 mg thrice daily for 10–14 days in mild to moderate cases.
- Oral vancomycin 125–500 mg 6 hourly for 14 days in severe cases.
- Oral vancomycin plus intravenous metronidazole in refractory cases.
- Intravenous vancomycin not effective.
- Oral probiotic therapy (use of live nonpathogenic bacteria to restabilise the gut flora and provide colonisation resistance against *C. difficile*) often used in resistant or relapsed cases. Probiotics use organisms resistant to gastric acid. *Lactobacillus acidophilus* and *Saccharomyces boulardii* produce proteases that digest *C. difficile* toxins. However, clinical benefits not shown; may rarely produce septicaemia.
- Antimotility drugs (loperamide or diphenoxylate) should not be given as they can precipitate toxic megacolon.
- Colectomy in severely ill, refractory patients.

Prevention

- Hand washing, glove use, isolation of patients in a single room, barrier precautions and cleaning of the physical environment throughout the duration of symptomatic disease.

- Healthcare workers should wash their hands with soap and water, rather than with alcohol-based hand sanitising agents because alcohol is ineffective in killing *C. difficile* spores.

Q. Briefly explain Gardner's syndrome.

• Autosomal dominant disorder	• Benign soft tissue tumours like lipomas, fibromas and sebaceous cysts
• Numerous adenomatous polyps in colon	• Osteomas, particularly involving jaw and skull
• Few gastric and duodenal polyps	• Treatment is prophylactic total colectomy for fear of carcinoma colon

Q. Give a brief account of Peutz–Jeghers syndrome.

• Autosomal dominant disorder	• Tumours of ovary, breast, pancreas, lung and endometrium in some cases
• Multiple hamartomatous polyps of the entire GIT but mainly in small intestine	• Malignant potential of polyps
• Pigmentation of skin, lips and buccal mucosa	• Diagnosis and treatment by intraoperative enteroscopy (IOE) and double balloon enteroscopy (DBE) to remove all small intestinal polyps
• Anaemia, rectal bleeding, abdominal pain, intestinal obstruction, intussusception	• Follow-up surveillance for various cancers by periodic colonoscopy, upper endoscopy, capsule endoscopy, CT, MRI or ultrasound of the pancreas, chest X-ray, mammography and pelvic examination with ultrasound in women, testicular examination in men, carbohydrate antigen 19-9 (CA 19-9) and cancer antigen (CA-125)

Q. Discuss briefly the psychosomatic disorders of the gastrointestinal tract.

Q. Describe the aetiology, clinical features, investigations and management of irritable bowel syndrome.

Definition

- A functional disorder of the gastrointestinal tract is one for which no structural, infective or biochemical cause can be found. A classification of the functional disorders of gastrointestinal tract is given below.

• Bad taste (cacogeusia) or foul smell of breath (halitosis)	• Globus hystericus
• Functional heartburn	• Aerophagia and unspecified excessive belching
• Non-cardiac chest pain due to oesophageal dysmotility	• Functional vomiting and cyclic vomiting syndrome
• Functional dyspepsia	• Irritable bowel syndrome
• Functional bloating	• Functional diarrhoea and functional constipation

Globus Hystericus

- Persistent or intermittent, nonpainful sensation of a lump or foreign body in throat.
- Occurrence of the sensation between meals (i.e. sensation is independent of swallowing).
- Absence of dysphagia or odynophagia.
- Absence of evidence that gastro-oesophageal reflux is the cause of the symptom.
- Absence of histopathology-based oesophageal motility disorders.

Functional or Psychogenic Vomiting

- May occurs in anxiety neurosis.
- Usually occurs on awakening or immediately after breakfast.
- In the young, it may be due to school phobia.

- Characterised by retching alone or vomiting of gastric secretions or food.
- Little or no weight loss.
- Exclude pregnancy, alcohol abuse, depression, CNS disorders, metabolic causes and chronic cannabis use.
- Treatment is basically of the underlying psychological disturbances, tranquillisers and antiemetics.

Irritable Bowel Syndrome

- Irritable bowel syndrome (IBS) is a benign, chronic symptom complex of altered bowel habits and abdominal pain.

Aetiology

- No organic cause can be found.
- Altered GI motility occurs in the form of exaggerated gastrocolic reflex, altered gastric emptying, increased small bowel contractions and increased small intestinal transit.
- Neurotransmitters such as serotonin may be an important factor. It stimulates intestinal secretion and peristalsis in addition to visceral pain receptors via $5-HT_3$ and $5-HT_4$ pathways. Serotonin signalling is terminated by a specific serotonin reuptake transporter (SERT) located on enterocytes within the intestinal mucosa. A decrease in SERT leads to increased serotonin concentrations at the receptors.
- Psychological disturbances like anxiety, tension and excessive worry are all aetiologically significant.
- Certain foods may precipitate an attack.

Clinical Features

- Three clinical variants:
  - Those with spastic colitis, having primarily chronic abdominal pain and constipation (IBS with constipation or constipation-predominant IBS—at least 25% of stools are hard and fewer than 25% are loose or watery).
  - Those with chronic intermittent, watery diarrhoea often without pain (IBS with diarrhoea or diarrhoea-predominant IBS—at least 25% of stools are loose or watery and fewer than 25% are hard).
  - Those with both features and alternating diarrhoea and constipation (mixed IBS—at least 25% of stools are loose or watery and at least 25% are hard).
- More common in females of the age group 20–40 years.
- Abdominal pain is the most common symptom. Pain is referred to left or right iliac fossa or hypogastrium.
- Pain often provoked by food and relieved by defecation.
- Diarrhoea is often painless, occurs in the morning but never at night.
- In constipation-predominant IBS, stools are described as pellet like, ribbon like or pencil like.
- Mucus may or may not be present.
- Postprandial tenesmus is common, due to an exaggerated gastrocolic reflex.
- Other symptoms are abdominal distension, feeling of incomplete evacuation of rectum, excessive flatus, dyspepsia, heart burns, frequency and dysuria.
- Extraintestinal symptoms frequent and include headache, back pain, fatigue, myalgia, dyspareunia and urinary frequency.
- Physical examination is usually negative except for a tender sigmoid full of faeces and empty rectal ampulla.

Investigations

- Prime aim of investigations is to exclude organic bowel diseases.
  - Stool examination for leucocytes, parasites, ova, and occults blood
  - Routine testing for coeliac disease is advisable
  - Sigmoidoscopy
    - Usually normal or might show a prominent vascular pattern
    - Large amounts of mucus may be seen
    - Bowel shows marked motor activity
    - Difficulty in negotiating rectosigmoid curve due to spasm
  - Barium enema
    - Usually normal
    - Spasticity of sigmoid, accentuated haustral markings and a tubular appearance of the descending colon may be seen.
  - Exclude lactase deficiency, hyperthyroidism and alcohol abuse.

Diagnostic Criteria

Rome III Criteria

Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months (with symptom onset at least 6 months prior to diagnosis) associated with two or more of the following:
- Improvement with defecation
- Onset associated with a change in frequency of stool
- Onset associated with a change in appearance of stool

Other symptoms that are not essential but support the diagnosis of IBS:
- Abnormal stool frequency (>3 bowel movements/day or <3 bowel movements/week)
- Abnormal stool form (lumpy/hard or loose/watery stool)
- Abnormal stool passage (straining, urgency or feeling of incomplete bowel movement)
- Passage of mucus
- Bloating or feeling of abdominal distension

Treatment

- Reassurance of the patient and explanation for the symptoms.

Constipations-Predominant IBS

- Increase the roughage content of the diet and add a bulk laxative (methylcellulose, isab gol husk, psyllium and corn fibre).
- Prokinetic agents like mosapride and levosulpiride are not useful in most patients.
- Tegaserod, a 5-HT$_4$ agonist and a prokinetic drug, stimulates intestinal secretion of water and chloride and decreases the nociceptive response to rectal distension. However, its use is restricted to women below 55 years with no cardiovascular morbidity, who are severely distressed due to symptoms (including pain), and who are educated about possible side effects, particularly severe diarrhoea and ischaemic cardiovascular events.
- Osmotic agents like polyethylene glycol, lactulose and milk of magnesia may be tried, if fibre supplementation fails.
- A laxative lubiprostone, which acts as a chloride channel activator to increase water secretion into the faeces, can be used in women. Another intestinal secretagogue, linaclotide, is an agonist of guanylate cyclase (GC-C). It activates GC-C receptors on intestinal enterocytes causing chloride channel activation.
- If abdominal pain is not adequately relieved, give a short-term trial of an anticholinergic agent (dicyclomine 10 mg TID) or an antispasmodic (mebeverine 135 mg TID).
- Psychotropic agents like amitriptyline (10–25 mg initially) may be useful in patients with abdominal pain.

Diarrhoea-Predominant IBS

- Give loperamide (2–4 mg up to four times a day).
- Cholestyramine (4 g four to six times a day), a bile acid-sequestrating agent, is a second-line agent. This is because bile acid malabsorption is seen in up to one-third of patients.
- 5-HT$_3$ receptors antagonists inhibit GI motility and benefit abdominal pain by reducing visceral sensitivity. Ondansetron, granisetron, alosetron and cilansetron are all selective 5-HT$_3$. Alosetron can produce severe ischaemic colitis and is approved for women with severe symptoms not responding to other treatment. It is contraindicated in patients with constipation.
- Rifaximine may be helpful in the treatment for bloating and may relieve global symptoms.
- Probiotics may be useful in some patients.
- Anticholinergics for pain control.

Q. Describe the aetiology, pathology, clinical features, complications, differential diagnosis, investigations and treatment of abdominal tuberculosis.

- Abdominal tuberculosis indicates tubercular involvement of gut, abdominal lymph nodes, peritoneum, either individually or in various combinations.
- Intestinal tuberculosis commonly affects ileocecal region in 70% of patients. This is possibly related to:
  - Increased physiological stasis
  - Increased rate of fluid and electrolyte absorption
  - Minimal digestive activity
  - Abundance of lymphoid tissue
- Other areas that can get affected include ascending colon, jejunum, sigmoid colon, rectum, duodenum, stomach and oesophagus.

Aetiology

- *Mycobacterium tuberculosis.*

Routes of Spread

- Intestinal tuberculosis
  - Haematogenous spread from the primary lung focus in childhood, with later reactivation
  - Ingestion of bacilli in sputum from active pulmonary focus
  - Direct spread from adjacent organs
  - Through lymph channels from infected nodes
- Peritoneal tuberculosis
  - Spread from lymph nodes
  - Spread from intestinal lesions
  - Spread from tubercular salpingitis in females

Pathology

Intestinal Tuberculosis

- Three types
- Ulcerative (60%)
  - Found more often in malnourished adults.
  - Multiple superficial ulcers are largely confined to the epithelial surface of the ileocecal area.
  - Long axis of ulcers perpendicular to the long axis of the gut segment involved (CF in typhoid fever, long axis of intestinal ulcers lies parallel to the long axis of the segment involved).
  - Cicatrical healing of these circumferential ulcers results in strictures. Occlusive arterial changes may produce ischemia and contribute to the development of strictures.
  - Rarely, endarteritis may produce massive bleeding.
- Hypertrophic (10%)
  - Seen in ileocecal tuberculosis.
  - Found more often in relatively well nourished adults.
  - Consists of scarring, fibrosis, along with local hypertrophic mass. Can be confused with malignancy.
- Ulcero-hypertrophic (30%)
  - Combination of both hypertrophic and ulcerative forms.
  - Presents with a right iliac fossa lump constituted by hypertrophic ileocecal area, mesenteric fat and lymph nodes.

Peritoneal Tuberculosis

- Peritoneum is studded with multiple yellow-white tubercles.
- Peritoneum is thick and hyperaemic with a loss of its shiny lustre.
- The omentum is also thickened.
- Occurs in three forms:
  - Wet type presents with ascites.
  - Encysted (loculated) type presents with a localised abdominal swelling.
  - Fibrotic type presents with abdominal masses composed of mesenteric and omental thickening, with matted bowel loops felt as lumps in the abdomen. Adhesions may involve the bowel loops producing subacute intestinal obstruction.
  - A combination of these types is also common.

Lymph Nodal Tuberculosis

- Involvement of mesenteric, omental, periportal, peripancreatic lymph nodes.
- Nodes may become palpable as rounded masses (tabes mesenterica).
- Usually seen in young adults.
- May be confused with lymphoma.

Clinical Features

- Predominantly seen in young adults
- Clinical presentation is acute, chronic or acute on chronic
- Common symptoms include fever, pain, diarrhoea, constipation, alternating constipation and diarrhoea, weight loss, anorexia and malaise

- Pain either colicky due to luminal compromise or dull and continuous, when the mesenteric lymph nodes are involved
- Abdominal examination may reveal no abnormality or a doughy feel
- A well defined, firm, usually mobile mass is often palpable in the right lower quadrant of the abdomen
- Associated lymphadenitis produces mass
- Abdominal distention due to ascites

Complications

- Haemorrhage
- Perforation
- Subacute intestinal obstruction
- Fistula formation (between skin and intestine or between two loops of intestines)
- Malabsorption (ileocecal tuberculosis common cause of malabsorption in India). Various causes of malabsorption include:
  - Bacterial overgrowth in a stagnant loop
  - Bile salt deconjugation
  - Diminished absorptive surface due to ulceration
  - Involvement of lymphatics and lymph nodes

Differential Diagnosis

- Tropical sprue
- Amoebiasis
- Worm infestation
- Lymphoma
- Crohn's disease
- Colonic malignancy

Investigations

- Raised ESR, anaemia and hypoalbuminaemia
- Chest X-ray
  - May show evidence of active or old tubercular lesion
- Plain X-ray of abdomen
  - Calcified lymph nodes
  - Dilated bowel loops with multiple air–fluid levels due to obstruction
  - Air under diaphragm and dilated loops due to perforation
- Barium meal
  - May show hypermotility (accelerated intestinal transit)
  - Hypersegmentation of the barium column ("chicken intestine")
  - Precipitation, flocculation and dilution of the barium
  - Luminal stenosis with smooth but stiff contours ("hour glass stenosis")
  - Multiple strictures with segmental dilatation of bowel loops
  - Stierlin sign—a defect characterised by failure of the diseased segment to retain barium that is otherwise normally retained by adjacent uninvolved segments. Appears as a narrowing of terminal ileum with rapid emptying into a shortened caecum.
  - String sign—a thin stream of barium seen in the terminal ileum
- *Note:* Both Stierlin and String signs can also be seen in Crohn's disease, and hence, are not specific for tuberculosis.
- Barium enema.
  - Wide gaping of ileocecal valve with narrowing of the terminal ileum ("Fleischner" or "inverted umbrella sign")
  - Fold thickening and contour irregularity of terminal ileum shrunken in size ("conical caecum")
  - Pulled up caecum due to contraction and fibrosis of the mesocolon
  - Loss of normal ileocecal angle and dilated terminal ileum, appearing suspended from a retracted, fibrosed caecum ("goose neck deformity")
  - Localised stenosis opposite the ileocecal valve with a rounded off smooth caecum and a dilated terminal ileum ("purse string stenosis")
- Abdominal ultrasound
  - Intra-abdominal fluid (free or loculated; with or without debris and septae)
  - Localised fluid between radially oriented bowel loops due to local exudation from the inflamed bowel (interloop ascites; "Club sandwich" or "sliced bread" sign)

- Lymphadenopathy, discrete or matted with heterogenous echotexture due to caseation
- Uniform and concentric bowel wall thickening in the ileocecal region (versus eccentric thickening at the mesenteric border found in Crohn's disease and variegated appearance of malignancy)
- Contrast-enhanced CT scan
  - Symmetric circumferential thickening of caecum and terminal ileum
  - Regional lymph nodes
  - Mesenteric thickening
  - Ulceration or nodularity within the terminal ileum, along with narrowing and proximal dilatation
  - Ascitic fluid of high attenuation value
  - Thickened peritoneum and enhancing peritoneal nodules
  - Omental thickening seen as an omental cake appearance
  - Caseating lymph nodes with hypodense centres and peripheral rim enhancement
  - Retroperitoneal nodes (periaortic and pericaval) almost never seen in isolation, unlike lymphoma
- Ascitic fluid examination
  - See "ascites".
- Biopsy of peritoneum
  - Punch
  - Laparoscopic
- Colonoscopy
  - Mucosal nodules and ulcers in colon
  - Biopsy from the edge of ulcers

Treatment

- Antitubercular treatment similar to treatment of pulmonary tuberculosis
- Surgery
  - Strictureplasty for strictures that reduce the lumen by 50% or more and that cause proximal dilation.
  - Resection of segment having multiple strictures
  - Treatment of perforation

Q. Enumerate the conditions causing ulcers in intestine.

• Enteric fever	• Gram-negative bacillary dysentery
• Tuberculosis	• Zollinger–Ellison syndrome
• Amoebiasis	• Malignant ulcers
• Ulcerative colitis	• Mesenteric artery occlusion
• Crohn's disease	• Ischaemic colitis

Q. What are the inflammatory bowel diseases?

Q. Give the aetiology, pathology, clinical features, investigations and treatment of ulcerative colitis.

- Inflammatory bowel diseases are chronic inflammatory disorders of gastrointestinal tract characterised by a relapsing and remitting course.
- Inflammatory bowel diseases include several conditions, most common being:
  - Ulcerative colitis
  - Crohn's disease
- Other uncommon inflammatory bowel diseases include:
  - Microscopic ulcerative colitis
  - Microscopic lymphocytic colitis
  - Microscopic collagenous colitis

Ulcerative Colitis

Definition

- Ulcerative colitis is an inflammatory disease affecting mainly the large intestine, characterised clinically by recurrent attacks of bloody diarrhoea and pathologically by diffuse inflammation of colonic mucosa.
- Disease extent can be broadly divided into distal and more extensive disease.
  - Distal disease refers to colitis confined to the rectum (proctitis) or rectum and sigmoid colon (proctosigmoiditis).

- More extensive disease includes "left-sided colitis" (up to the splenic flexure), "extensive colitis" (up to the hepatic flexure) and pancolitis (affecting the whole colon).

Aetiology

- Familial or genetic
  - Strong family history
  - Occurrence in monozygotic twins
- Infectious
  - Possible pathogens include:
    - Mycobacterium (*M. avium paratuberculosis*)
    - Measles virus
    - Listeria monocytogenes
    - Yeast
    - Endogenous bacteria
      - *Bacteroides*
      - *E. coli*
- Dietary factors
  - Deficiency or excess of certain nutrients (butyric acid, sulphides, L-arginine and glutamine)
- Smoking
  - Patients with Crohn's disease are more likely to be smokers and smoking can exacerbate it.
  - There is an increased risk of ulcerative colitis in non-smokers.
- Psychological
  - Characteristic personality and major psychological stresses are related to flare-ups and precipitation of symptoms.
- Defective immune regulation
  - Many immunological abnormalities have been described that include stimulation of macrophages leading to excessive production of cytokines (interleukin-1, interleukin-6 and tumour necrosis factor-α). There is also activation of other cells (eosinophils, mast cells and fibroblasts).
  - Immune complexes may be responsible for extraintestinal manifestations.

Pathology

- Primarily involves the colonic mucosa.
- Mucosal involvement is uniform and continuous with no intervening areas of normal mucosa.
- Rectum is involved in 95% of cases (proctitis).
- From the rectum the disease extends proximally into the colon in a continuous fashion.
- Back wash ileitis is involvement of a few centimetres of ileum, when the entire colon is involved.
- Macroscopically, the mucosa appears hyperaemic, haemorrhagic or ulcerated. Ulcers do not usually extend deeper beyond the submucosa.
- "Pseudopolyps" are regenerating islands of mucosa surrounded by areas of ulceration and denuded mucosa. They protrude into the lumen of colon like polyps.
- Microscopically, the lamina propria is infiltrated with lymphocytes and plasma cells. There is loss of goblet cells also.
- Crypt abscesses are characteristic with infiltration of crypts with neutrophils.
- In toxic megacolon, transverse colon is dilated, walls are thin, mucosa denuded and inflammation extends to serosa. It may rupture later.
- In the chronic variety, there is fibrosis and shortening of the colon with loss of normal haustral pattern. The surface epithelium may show features of dysplasia.
- Strictures, anal fissures and anal abscesses are uncommon.

Clinical Features

- General
  - Severity of symptoms reflects the extent of colonic involvement and the intensity of inflammation
  - Exacerbations and remissions are characteristic
  - Bloody diarrhoea with mucus and pus
  - Abdominal pain, especially lower abdominal
  - Fever, weight loss and loss of appetite
  - Symptoms and signs of dehydration and anaemia

- Extraintestinal manifestations occur in one-third of patients which may be present even, when the disease is inactive (refer later)
- Tenderness on palpation over the colon, especially in the left iliac fossa. Relapses are associated with emotional stress, intercurrent infections and use of antibiotics.
- Incidence of carcinoma of colon is high, especially in cases of total colitis, duration more than 10 years and early age of onset.
- Acute variety
  - Disease involves the entire colon
  - Severe systemic symptoms like fever, weight loss and loss of appetite
  - Exhausting diarrhoea and dehydration
  - Tachycardia and postural hypotension
  - Tenesmus, lower abdominal pain and left iliac fossa tenderness due to serosal involvement
  - Toxic megacolon and rupture may occur (refer later)
- Chronic variety
  - Bowel is permanently damaged by fibrosis. Colon behaves as a rigid tube incapable of absorbing fluids, acting like a faecal reservoir
  - No systemic manifestations or toxaemia
  - Patient lives in chronic ill health with chronic diarrhoea
- Disease confined to rectum (proctitis)
  - Systemic symptoms are trivial or absent
  - Loose motions and blood streaking of stools
  - Severe tenesmus and frequent small loose stools
  - Bleeding and mucus per rectum
- Distal colitis
  - Constipation rather than diarrhoea
  - Retention of faeces in the proximal colon and small hard stools

Investigations

- Anaemia, raised ESR and leucocytosis
- Electrolyte abnormalities
- Hypoproteinaemia
- Abnormal liver function tests
- Blood culture in septicaemia
- Stool examination and culture to exclude infective pathology
- Stool for *Clostridium difficile* toxin
- Elevated faecal calprotectin and lactoferrin levels
- Plain radiograph of abdomen
  - To exclude toxic dilatation of colon
  - May help assess disease extent in ulcerative colitis
- Barium enema
  - Earliest features are irritability and incomplete filling
  - Ulcerations
  - Pseudopolyps and strictures
  - Chronic stage of the disease is characterised by shortening of the bowel, depression of flexures, narrowing of bowel lumen and rigidity. The bowel has asymmetric, ahaustral and tubular (pipe stem) appearance
- Sigmoidoscopy
  - Uniform continuous involvement of the mucosa
  - Loss of mucosal vascularity
  - Diffuse hyperaemia or erythema
  - Exudate of mucus, pus and blood
  - Mucosal friability—gentle rubbing of the mucosa with a cotton swab shows the appearance of diffuse, small bleeding points
  - Shallow, but small or confluent ulcers
  - Pseudopolyps
- Colonoscopy
  - For mild to moderate disease colonoscopy is preferable to flexible sigmoidoscopy because the extent of disease can be assessed. In moderate to severe disease, there is a higher risk of bowel perforation and flexible sigmoidoscopy is safer.

- Rectal biopsy shows mucosal inflammation
- Serologic markers
  - Perinuclear antineutrophilic cytoplasmic antibody (p-ANCA) is positive in 60–70% of patients with ulcerative colitis (seen in only 5–10% of patients with Crohn's disease).
  - Anti-*Saccharomyces cerevisiae* antibodies (ASCA) in only 10–15% cases (positive in 60–70% case of Crohn's disease).
  - Anti-goblet cell autoantibodies in 30–40% cases of ulcerative colitis and Crohn's disease.

Treatment

General Measures

- Parenteral nutrition through a central venous line in seriously ill patients
- High-protein and low-residue diet
- Blood and plasma infusions
- Correction of dehydration and electrolyte imbalance
- Parenteral broad-spectrum antibiotics in septicaemia
- Codeine phosphate and loperamide for mild diarrhoea (avoided in severe disease)

Corticosteroids

- For inducing remission in moderate to severe cases
- No role in maintaining remissions
- Local treatment
  - Hydrocortisone or prednisolone enemas, suppositories or foam.
  - Choice of topical formulation is determined by proximal extent of the inflammation (suppositories for disease of the rectosigmoid junction; foam or liquid enemas for more proximal disease).
  - Duration of treatment is 3–6 weeks.
  - Proctitis is treated with corticosteroid suppositories twice daily.
  - Distal colitis with mild symptoms is treated with corticosteroid enema once or twice daily.
  - Topical steroids are less effective than topical 5-aminosalicylic acid (5-ASA).
- Systemic treatment
  - Prednisolone 40–60 mg orally daily for 3–6 weeks.
  - Intravenous hydrocortisone 100–200 mg 6 hourly in severe cases.
  - Intramuscular or subcutaneous injection of long-acting corticotrophin is used in the treatment of relapses.
  - Steroids once started are gradually tapered and withdrawn.

Aminosalicylates

- Useful in controlling acute exacerbation as well as to prevent relapses. Maintenance therapy may reduce the risk of colorectal cancer by up to 75%.
- Available as oral tablets, sachets, liquid or foam enemas.
- Act on epithelial cells by a variety of mechanisms to moderate the release of lipid mediators, cytokines and reactive oxygen species.
- Include 5-aminosalicylic acid (5-ASA) or mesalazine alone, or combination of 5-ASA with a carrier, which releases 5-ASA after splitting by bacteria in colon (sulphasalazine, olsalazine and balsalazide).
- Sulphasalazine, the most frequently used agent, is a combination of:
  - 5-ASA (active agent)
  - Sulphapyridine (acting as a "carrier")
- The compound is broken down in colon by bacterial action liberating 5-ASA that acts locally.
- Side effects include nausea, headache, rashes, sterility in males, haemolytic anaemia, Stevens–Johnson syndrome and agranulocytosis. Dose is given 2–4 g/day in mild to moderate attack and 0.5 g QID to prevent relapses, as a maintenance.
- Mesalazine uses 5-ASA with an enteric coating.
- Azodisalicylate joins two molecules of 5-ASA by an azo bond that is split by bacteria in the colon. An example is olsalazine. A side effect unique to olsalazine is diarrhoea resulting from excessive production of fluid in the intestines (secretory diarrhoea).
- In disease limited to rectosigmoid, topical (as enema or foam) 5-ASA (1 g per day) may be tried before resorting to topical steroids.

Note: 5-ASA in free form is absorbed in the small intestine and may produce renal toxicity.

Immunosuppressive Agents

- Azathioprine and 6-mercaptopurine both are useful in maintaining remission and have steroid sparing properties. Long-term treatment is required to prevent relapse.
  - Useful in patients, who require two or more corticosteroid courses within a calendar year; those whose disease relapses as the dose of prednisolone is reduced below 15 mg, or relapse within 6 weeks of stopping steroid.
- Methotrexate useful in patients, who do not respond to azathioprine.
- Cyclosporin—an inhibitor of calcineurin, prevents clonal expansion of T-cell subsets. Intravenous cyclosporin is effective in severe ulcerative colitis refractory to steroids. After response, azathioprine or 6-mercaptopurine is required to maintain remission.
- Mycophenolate mofetil, which suppresses the proliferation of B and T cells, is effective in maintaining remission.
- Tacrolimus has shown efficacy in refractory or extensive disease.
- In patients resistant to immunosuppressives, infliximab (anti-TNF-α antibody) has been shown to be effective.

Surgical Management

- Emergency surgical procedure is colectomy with ileostomy; the rectum and distal colon being removed at a later stage.
- Elective surgical procedure is total proctocolectomy with ileostomy or ileorectal anastomosis or ileo-anal anastomosis.

Indications of emergency surgery	Indications of elective surgery
- Severe forms of the disease - Toxic dilatation of colon - Perforation - Severe haemorrhage	- Acute disease that fails to respond to medical treatment - Frequent relapses in spite of adequate treatment - Chronic disease with permanently damaged bowel; strictures - Total bowel involvement with activity extending over >10 years

Miscellaneous

- Colonoscopy with multiple biopsies is recommended every 3 years in patients with extensive colitis of more than 10 years' duration to assess for any dysplastic or malignant changes. In those with disease for more than 20 years, colonoscopy is recommended every 2 years and after that, every year. Four random biopsies every 10 cm from the entire colon are best taken with additional samples of suspicious areas. If the biopsy shows high-grade dysplasia, total colectomy may be done.
- Newer methods for targeted biopsies include chromoendoscopy, narrow band imaging or confocal endomicroscopy.

Q. Discuss the aetiology, pathology, clinical features, investigations and management of Crohn's disease.

Definition

- Crohn's disease is characterised by patchy and transmural inflammation, which may affect any part of the gastrointestinal tract.
- It may be defined by location (terminal ileal, colonic and ileocolic, upper gastrointestinal) or by pattern of disease (inflammatory, fistulating or stricturing).

Aetiology

- Factors listed under "ulcerative colitis".

Pathology

- Affects small and large bowels, but more common in small bowel. Can affect any part of the gastrointestinal tract from mouth to anus.
- Commonly involved sites in the order of frequency are:
  - Terminal ileum and right side of colon
  - Colon alone
  - Terminal ileum alone
  - Ileum and jejunum
- Inflammation extends through all the layers of the intestinal wall.
- Characteristically the involvement is discontinuous. Involved segments of intestine are separated from each other by intervening segments of normal bowel.
- Bowel wall is greatly thickened and leathery with the lumen narrowed (stenosis).
- Mucosa has a nodular cobble stoned look.

- Mucosal involvement is characteristically patchy. The inflammatory process is interrupted by islands of normal mucosa. A small lesion separated from a major area of involvement is known as a "skip lesion".
- Fistulae develop between adjacent loops of intestine or between affected segments of intestine and the bladder, uterus, vagina or perineum.
- The intestinal ulcers may penetrate to form intra-abdominal abscesses.
- Mesentery and regional lymph nodes are involved.
- Microscopically, the characteristic feature is non-caseating granuloma formation.

Clinical Features of Crohn's Disease of Small Intestine or Ileum and Right Colon (Ileocolitis)

- Chronic disease with exacerbations and remissions
- Young adults with history of fatigue, weight loss, diarrhoea, fever and pallor
- Abdominal pain occur due to peritoneal involvement or intestinal obstruction
- Right lower quadrant pain, tenderness, guarding and mass
- Mass palpable per abdomen and rectally reflects adherent loops of intestine and abscess
- Recurrent episodes of colicky abdominal pain with nausea, vomiting and excessive borborygmi suggest subacute intestinal obstruction
- Stool usually does not contain frank blood, mucus or pus unless colon is involved
- Anal lesions such as oedematous skin tags, fistulae, fissures, perianal and perirectal abscesses are characteristic of the disease
- Features of malabsorption like weight loss and anaemia (iron, folic acid and B_{12} malabsorption)
- Sodium, potassium, water, magnesium and zinc deficiency due to chronic diarrhoea

Intra-abdominal complications

- Intestinal obstruction
- Fistula formation
  - Ileovesical fistula leads to recurrent urinary infection, cystitis and pneumaturia
  - Fistulae between contiguous segments of intestines
  - Cutaneous fistulae
- Abscesses
- Free perforation
- Rectal fissures
- High incidence of carcinoma of intestine
- Gastric outlet obstruction or duodenal obstruction
- Gallstones and urinary oxalate stones
- Secondary amyloidosis in long-standing cases (hepatosplenomegaly with proteinuria)

Investigations

- Normochromic normocytic or macrocytic or hypochromic anaemia
- Raised ESR and leucocytosis
- Abnormal liver function tests
- Hypoproteinaemia
- Stool culture and routine examination to exclude infectious causes of diarrhoea
- Schilling test for malabsorption of vitamin B_{12}
- Sigmoidoscopy and colonoscopy
  - Segmental involvement with intervening normal area
  - Ulcerations and deep longitudinal fissures. Cobble-stone appearance of mucosa
  - Rectal sparing
- Biopsy of colonic mucosa, ileal mucosa, anal skin tags and perianal inflammatory lesions will show typical granulomatous inflammation. Tuberculosis must be excluded by appropriate histological tissues
- Barium meal follow through and barium enema
  - Rectal sparing
  - Skip lesions
  - Involvement of terminal ileum
  - Loss of mucosal details and rigidity of involved segments
  - Radiologic cobble-stone appearance of mucosa
  - Fistulous tracts, especially in ileocecal area
  - Multiple strictures
  - "String sign" due to marked narrowing of a segment of affected bowel
- High-resolution ultrasound and spiral CT scanning helpful in defining thickness of the bowel wall and intra-abdominal abscesses.
- Radionuclide scan using gallium-labelled polymorphs or indium-labelled leucocytes to identify intestinal and colonic disease and localise extraintestinal abscesses.

- Serologic markers
  - Perinuclear antineutrophilic cytoplasmic antibody (p-ANCA) is seen in only 5–10% of patients with Crohn's disease (positive in 60–70% of patients with ulcerative colitis).
  - Anti-*Saccharomyces cerevisiae* antibodies (ASCA) positive in 60–70% cases of Crohn's disease (positive in only 10–15% cases of ulcerative colitis).
  - Antigoblet cell autoantibodies in 30–40% cases of Crohn's disease.
  - Antiglycan antibodies in about 40–50% cases (e.g. antilaminaribioside and antimannobioside antibodies)

Treatment

- Diet and nutrition
  - High-protein and high-energy diet
  - Enteral feeding by nasogastric tube. Total parenteral nutrition in very ill patients
  - Plasma or blood transfusion
  - Low residue diet in colic and subacute obstruction
  - Low-fat diet and low linoleic acid in diet
  - Milk-free diet in lactose intolerance
  - Antibiotics for bacterial colonisation of gut
  - Supplementation of iron, folic acid, calcium, zinc, vitamins D, B_{12}, and electrolytes
- Drug treatment
  - Loperamide or codeine for diarrhoea.
  - In long-standing cases, diarrhoea may be due to bile salt malabsorption. Cholestyramine should be tried in such cases.
  - 5-ASA (e.g. mesalazine 4 g/daily or sulphasalazine 2 g twice daily) as maintenance in mild to moderate ileocolonic disease. However, its benefits in maintaining remission are not clear.
  - Prednisolone 40–60 mg daily initially, which is gradually tapered and withdrawn.
  - The use of immunosuppressive agents (azathioprine, 6-mercaptopurine, methotrexate and cyclosporin) and newer agents (mycophenolate mofetil, tacrolimus and infliximab) has been discussed under "ulcerative colitis". Another TNF-α blocker is adalimumab.
  - Natalizumab, a monoclonal antibody directed against α4 integrins, is effective for induction and maintenance of remission in patients with moderate to severe Crohn disease, when therapy with TNF-α blocker has failed. It can produce progressive multifocal leukoencephalopathy.
  - Another agent is oral budesonide, a corticosteroid with minimal absorption and therefore, minimal systemic exposure.
  - Metronidazole is given 400 mg BD in perineal Crohn's disease.
- Surgical treatment
  - Indicated in repeated episodes of subacute obstruction, abscess, perforation, extensive and severe involvement of colon.
  - Minimal resections for strictures and fistulae.

Q. Give a brief account of toxic dilatation of colon (toxic megacolon).

- Toxic dilatation of colon occurs most commonly in ulcerative colitis. In fact, it is a severe form of ulcerative colitis with an additional feature of colonic dilatation. It is thought that neuromuscular tone of bowel is affected resulting in dilatation. Drugs like codeine, diphenoxylate, loperamide and anticholinergics used in the treatment of diarrhoea can precipitate this complication. Barium enema is another precipitating factor.

Clinical Features

- Clinical features of severe colitis.
- High fever, tachycardia, dehydration, electrolyte imbalance and abdominal pain.
- Patient is toxic and ill.
- Examination reveals colonic dilatation and severe abdominal tenderness.
- Wall of the colon is thin and may rupture.
- Transverse colon is most commonly involved.
- Plain radiograph of abdomen may show colonic dilatation with transverse colonic diameter more than 5.5 cm. Air may be seen in the wall of the colon.

Q. What are the complications of inflammatory bowel disease?

- Complications of inflammatory bowel disease are classified as local and systemic (extraintestinal).

Local complications

- Fistulae, abscess and strictures
- Perforation
- Toxic dilatation (toxic megacolon)
- Carcinoma (cumulative risk is 5% after 20 years and 12% after 25 years in ulcerative colitis)

Systemic (extraintestinal) complications

- Nutritional and metabolic
  - Weight loss and anaemia
  - Electrolyte imbalance
  - Hypoalbuminaemia
- Eyes
  - Iritis and uveitis
  - Episcleritis and conjunctivitis
- Hepatobiliary
  - Fatty liver
  - Gallstones
  - Pericholangitis
  - Sclerosing cholangitis
  - Bile duct carcinoma
  - Chronic hepatitis
  - Cirrhosis
  - Amyloidosis

- Musculoskeletal
  - Ankylosing spondylitis
  - Seronegative arthritis
  - Sacroiliitis
- Skin and mucous membranes
  - Erythema nodosum
  - Pyoderma gangrenosum
  - Aphthous stomatitis
  - Finger clubbing
- Haematological
  - Venous thrombosis; thromboembolism
  - Autoimmune haemolytic anaemia
- Renal
  - Calculous disease
  - Amyloidosis
  - Pyelonephritis

Q. Differentiation of ulcerative colitis from Crohn's disease of the colon?

Pathologic Features

Ulcerative colitis	Crohn's disease
• Continuous involvement	• Segmental involvement
• Inflammation is mucosal and submucosal	• Inflammation is transmucosal
• Granulomas are absent	• Granulomas are common
• Crypt abscesses are common	• Crypt abscesses are uncommon
• Loss of goblet cells	• No loss of goblet cells
• Strictures, fissures and fistulae uncommon	• Strictures, fissures and fistulae are common
• No mesenteric and lymph nodal involvement	• Mesenteric and lymph nodal involvement are common

Clinical Features

Ulcerative colitis	Crohn's disease
• Rectal bleeding common	• Rectal bleeding is uncommon
• Abdominal pain is less common	• Abdominal pain is more common
• No palpable abdominal masses	• Palpable abdominal masses
• Fistulae, fissures and perianal skin tags are uncommon	• Fistulae, fissures and perianal skin tags are characteristic
• Small bowel involvement is uncommon	• Small bowel involvement is common
• Rectal and colonic involvement is common	• Rectal and colonic involvement is rare
• Toxic dilatation is relatively common	• Toxic dilatation is uncommon

Q. Discuss briefly about probiotics and prebiotics.

Probiotics

- Defined as live microbes or components of microbe, if administered in adequate amounts confer a beneficial physiological effect on the host.
- Probiotics are usually bacterial components of the normal human intestinal flora, for example, lactobacilli and bifido-bacteria, that produce lactate and short-chain fatty acids such as acetate and butyrate as end products of metabolism. *Saccharomyces boulardii*, a yeast is also an important probiotic.
- A commonly used probiotic is yoghurt in which, milk is fermented by bacteria that convert lactose into lactic acid.

- Probiotics are also available as freeze-dried bacteria in capsule, tablet or powder form. Their composition is variable but most contain *Lactobacillus acidophilus*, often with *Bifidobacterium*.

Prebiotics

- A selectively fermented ingredient that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit upon host health.
- Prebiotics are selected as being non digestible by the host and not metabolised by non-probiotic gut flora such as *Bacteroides* spp. and *Escherichia coli*.
- Synthetic prebiotics are oligosaccharides based on fructose or galactose, known as FOS (fructose-oligosaccharides) and GOS (galactose-oligosaccharides), respectively. Lactulose is also a prebiotic.
- Can be added to foods, or combined with a probiotic to make a symbiotic.

Potential Uses

- Probiotics helpful in normalising the nutritional status of malnourished children. Use of yoghurt suggested by the World Health Organisation for nutritional recovery. Probiotic species that show a positive effect include *L. acidophilus*, yoghurt organisms (*L. delbrueckii* var. *bulgaricus and Streptococcus salivarius* var. *thermophilus*), *L. plantarum* and *Bifidobacterium lactis*.
- Lactose intolerance, where yoghurt is preferred source of probiotics.
- Prebiotics like lactulose is useful in hepatic encephalopathy.
- Investigative role in preventing osteoporosis as prebiotics may increase calcium absorption.
- Chronic constipation and irritable bowel syndrome.
- Ulcerative colitis.
- Antibiotic-associated diarrhoea—probiotics containing *Saccharomyces boulardii* (a yeast) may be effective to some extent in the prevention and treatment of antibiotic-associated diarrhoea.
- Rotavirus-induced diarrhoea.
- Possible role in improving immunity.
- Necrotising enterocolitis in neonates.
- Reducing development of colonic cancer.

Safety

- The safety record of probiotics is remarkable. Nevertheless, there have been a few reports of bacteraemia.

Q. Discuss acute pancreatitis.

Aetiology

• Alcohol ingestion (acute and chronic)	• Infections
• Biliary calculus	• Viral hepatitis
• Post-operative (abdominal and non-abdominal)	• Mumps
• Post-ERCP*	• Roundworm
• Trauma to abdomen	• Mycoplasma
• Metabolic conditions	• Toxoplasma
• Renal failure	• Drugs
• Post-renal transplantation	• Sulphonamides
• Hypertriglyceridaemia	• Tetracyclines
• Hypercalcaemia	• Oestrogens
• Acute fatty liver of pregnancy	• Tamoxifen
• Penetrating peptic ulcer	• L-asparaginase
• Connective tissue diseases	• Azathioprine
• Systemic lupus erythematosus	• Thiazides
• Thrombotic thrombocytopaenic purpura	• Frusemide
• Polyarteritis nodosa	• Didanosine
	• Pentamidine
	• Valproic acid
	• Corticosteroids
	• Hereditary pancreatitis
	• Organophosphate poisoning

*Endoscopic retrograde cholangiopancreatography

Pathology

- Oedematous pancreatitis (diffuse enlargement of pancreas with lack of pancreatic parenchymal necrosis or peripancreatic necrosis evident on imaging).
- Necrotising pancreatitis (presence of tissue necrosis, either of pancreatic parenchyma or peripancreatic tissues; may be infected or sterile).
- Haemorrhagic pancreatitis.

Clinical Features

Symptoms

- The cardinal symptom of acute pancreatitis is pain.
  - Mild to severe intensity
  - Dull, boring and steady
  - Sudden pain in onset and gradually increases in severity
  - Usually located in the epigastric region, though may be perceived more on the left or right side, depending on which portion of the pancreas is involved.
  - Radiates directly through the abdomen to the back
  - Partial relief, if patients sit up and leans forwards
  - Lasts for more than 1 day
- Nausea and vomiting
- Anorexia

Signs

- Fever (low-grade)
- Tachycardia
- Tachypnoea (secondary to inflammation of lungs, atelectasis and pleural effusion)
- Hypotension (secondary to exudation of plasma in peritoneal cavity, kinin-induced vasodilatation, systemic effects of proteolytic and lipolytic enzymes released into circulation)
- Jaundice
- Abdominal tenderness, muscular guarding and distension
- Bowel sounds often hypoactive
- Lungs
  - Cyanosis
  - Basal crepitations
  - Pleural effusion
- Skin
  - Erythematous skin nodules due to focal subcutaneous fat necrosis.
  - Bluish discolouration around the umbilicus (Cullen's sign). Also seen with ruptured ectopic pregnancy, ruptured aortic aneurysm, ruptured spleen and hepatocellular carcinoma.
  - Bluish or green–brown discolouration in the flanks (Turner's sign) due to haemoperitoneum. Other causes include blunt abdominal trauma, ruptured abdominal aortic aneurysm, ruptured ectopic pregnancy and spontaneous bleeding secondary to coagulopathy.
  - Cullen's sign and Turner's sign indicate severe necrotising pancreatitis.
- Others
  - Haematemesis or melaena.
  - Ischaemic injury to retina is seen on fundus examination (Purtscher retinopathy).

Investigations

- Serum amylase
  - Levels increase for initial 24 hours and then decline to normal in 3–5 days.
  - Remains elevated in pancreatic abscess or pseudotumour formation.
  - Hypertriglyceridaemia occurs in 15–20% of patients with acute pancreatitis and serum amylase levels are often spuriously normal in such cases.

Causes of Elevated Serum Amylase

• Acute pancreatitis	• Mumps
• Small intestinal obstruction	• Diabetic ketoacidosis
• Perforation of peptic ulcer	• Burns
• Mesenteric ischemia	• Ectopic pregnancy
• Tubo-ovarian disease	• Pancreatic carcinoma
• Renal insufficiency	• Macroamylasaemia

- Serum lipase
  - Preferable for diagnosis as its elevation is more specific than that of amylase.
  - Lipase takes longer time to clear from the blood, so it is a more useful indicator of pancreatitis than amylase.
  - Marked elevation in pleural or peritoneal fluid (>5000 IU/dL) suggests pancreatitis.
- Other blood investigations
  - Blood glucose, total leucocyte count, platelet count, blood urea, serum calcium and other electrolytes, triglycerides.
  - Blood gases.
- Plain X-ray abdomen and chest
  - To exclude other causes of acute abdominal pain (e.g. perforation).
  - A gas-filled duodenum (sentinel loop) secondary to localised ileus may be seen.
  - Absence of gas in the transverse colon (colon cut-off sign).
  - If abscess forms in the necrotic pancreas, the X-ray may show multiple extraluminal gas shadows in the pancreatic area.
  - Calcification in pancreas in chronic pancreatitis.
- Ultrasound of abdomen
  - To evaluate gallbladder and biliary tree.
  - It can detect acute pancreatitis in more than 60% of cases. However, pancreatic evaluation may be obscured by bowel gas.
- CT scan of abdomen
  - May show solid mass of swollen pancreas (phlegmon), pseudocyst or pancreatic abscess.
- MRI abdomen
  - Greater sensitivity for detecting mild acute pancreatitis as compared with CT scan.
  - Highly effective at identifying fluid collections and pancreatic necrosis.
  - Magnetic resonance cholangiopancreatography (MRCP) can be performed at the same time and stones within common bile duct can be readily identified, if biliary pancreatitis is suspected.
- Endoscopic ultrasound (EUS)
  - Can be used to evaluate common bile duct for the presence of stones.
  - If stones are seen, ERCP can be performed at the same time to remove them.

Diagnosis

- Presence of at least 2 of the following criteria:
  - Abdominal pain characteristic of acute pancreatitis
  - Serum amylase and/or lipase ≥3 times the upper limit of normal
  - Characteristic findings of acute pancreatitis on computed tomography scan

Prognostic Features

Ranson Criteria

At admission	During initial 48 hours
• Age >55 years	• Fall in haematocrit >10% of baseline
• Leucocytosis >6000/cmm	• Fluid sequestration >4000 mL
• Blood sugar >200 mg/dL	• Hypocalcaemia <8 mg/dL
• Serum LDH >400 IU/L	• Hypoxaemia with paO_2 <60 mmHg
• Serum AST >250 IU/L	• Rise in blood urea >10 mg/dL after IV fluids
	• Hypoalbuminaemia <3.2 g/dL
0–2 Criteria – Mortality 2% 3–4 Criteria – Mortality 15% 5–6 Criteria – Mortality 40% More than 6 Criteria – Mortality 100%	

Differential Diagnosis

- Intestinal perforation
- Acute myocardial infarction
- Acute cholecystitis
- Pneumonia
- Acute appendicitis
- Bowel ischaemia

Complications

Local	Systemic
• Necrosis (sterile or infected)	• Hypovolaemic shock
• Pseudocyst	• Acute respiratory distress syndrome
• Pancreatic abscess	• Multiple organ failure
• Pancreatic ascites	• Renal failure
• Intraperitoneal haemorrhage	• Disseminated intravascular coagulation
• Obstructive jaundice	• Gastrointestinal haemorrhage
• Intestinal obstruction	• Fat necrosis
• Splenic vein thrombosis	• Hypocalcaemia
	• Pleural effusion

Treatment

- Nil orally initially with gradual return to oral intake as abdominal pain recedes and hunger returns. Enteral feeding should be restarted within 2–3 days even in severe cases.
- Intravenous fluids to maintain intravascular volume in the first few days.
- Pain control with analgesics
- Nasogastric aspiration if pain continues, patient has protracted vomiting or if obstruction is seen on plain X-ray abdomen
- Monitor pulse, blood pressure, abdominal girth, urine output, blood glucose and calcium, and blood gases. Severe cases should be monitored in intensive care units
- Antibiotics, carbapenems (imipenem or meropenem) or ceftazidime, in severe cases
- Other drugs include proton-pump inhibitors, glucagon, octreotide and aprotinin (protease inhibitor)
- Surgery is indicated for:
  - Infected pancreatic necrosis
  - Diagnostic uncertainty
  - Complications.
- ERCP within first 36–48 hours in patients with gallstone pancreatitis, who are in very severe group
- Most acute peripancreatic fluid collections and/or pseudocysts do not require interventions unless, they become infected or cause significant extrinsic compression of other organs.

Q. Discuss briefly about chronic pancreatitis.

- Chronic inflammation of pancreas presenting as recurrent pain, endocrine deficiency (diabetes mellitus), exocrine deficiency (malabsorption), or a combination of two or all three features.

Aetiology

• Chronic alcohol ingestion	• Cystic fibrosis
• Cholelithiasis	• Hypercalcaemia
• Cigarette smoke	• Hyperlipidaemia
• Drugs: valproate, thiazide, oestrogen, azathioprine	• HIV infection
• Stenosis of sphincter of Oddi	• Familial
• Autoimmune pancreatitis	• Idiopathic—tropical or calcific
• Associated with autoimmune diseases (Sjogren's syndrome, primary biliary cirrhosis)	

Clinical Features

- Pain, acute or recurrent, continuous or intermittent. May be referred to chest or back.
- Pain is often increased by alcohol or heavy meals.
- Features of local complications (e.g. pseudocyst, obstruction of adjacent organs, or vascular thrombosis).
- Features of malabsorption—diarrhoea, steatorrhoea, weight loss, features of fat-soluble vitamin deficiency and vitamin B_{12} deficiency (exocrine failure).
- Diabetes mellitus (endocrine failure).
- In late stages, mechanical obstruction of common bile duct can occur.

Investigations

- Serum amylase and lipase are usually normal.
- Hyperlipidaemia or hypercalcaemia (if cause of chronic pancreatitis is elevated calcium).
- Plain X-ray of abdomen.
  - Calcification in pancreatic area (in 30%).
  - Sensitivity for picking calcification increases, when both anteroposterior and oblique views are taken.
- Ultrasound abdomen and CT scan of abdomen.
  - Pancreatic atrophy
  - Calcifications
  - Dilatation of bile duct
  - Stricture of bile duct
- ERCP is the gold standard for diagnosis as it most accurately demonstrates pancreatic ducts.
- Magnetic resonance cholangiopancreatography (MRCP) may replace ERCP.
- Endoscopic ultrasound to evaluate pancreas.
- Pancreatic function tests.
  - Seceretin/cholecystokinin (CCK) stimulation test (reduction in bicarbonate and enzyme secretion).
  - Faecal chymotrypsin or elastase concentration
  - 24 hour faecal fat
  - Oral glucose tolerance test

Treatment

- Abstinence of alcohol.
- Diet rich in medium-chain triglycerides that do not require lipase for digestion.
- Pancreatic enzymes, particularly lipase, 20,000–75,000 U should be taken before each meal to reduce faecal fat excretion.
- Proton-pump inhibitors or H_2-blockers to prevent inactivation of pancreatic enzymes by gastric acid.
- Treatment of pain by opioids or NSAIDs. In intractable pain coeliac ganglion blockade may be tried.
- Steroids in autoimmune pancreatitis.
- Treatment of diabetes.
- Endoscopic therapy in painful chronic pancreatitis to allow pancreatic duct drainage in patients with obstructed ducts, and treatment of complications such as pseudocysts and bile duct obstruction with jaundice.
- Surgery for unremitting pain; includes pancreatectomy and pancreato-jejunostomy.

Q. Describe the features of tropical pancreatitis.

- It is a juvenile form of chronic calcific pancreatitis that is not related to alcohol intake.
- Seen almost exclusively in tropical countries.
- In India, it is more common in southern states (Kerala and Tamil Nadu).

Aetiology

- Various postulated aetiologies are:
  - Malnutrition
  - Diet rich in cassava that contains cyanogenic glycosides
  - Oxidant stress
  - Infections (Coxsackie and viral hepatitis)
  - Familial

Clinical Features

- Affects young people, generally males.
- Pursues a relatively accelerated course.
- Presents with recurrent abdominal pain, typically in epigastric area with radiation to back. Pain gets precipitated by heavy meals.
- Associated features include malnutrition, enlarged parotid glands, abdominal distention and a peculiar cyanotic hue of the lips.
- Pancreatic exocrine deficiency presents with steatorrhoea and malabsorption.
- Diabetes mellitus is common. Even without insulin ketosis is uncommon. Episodes of hypoglycaemia with insulin are frequent.

Investigations

- Plain X-ray and ultrasound of abdomen show multiple and large intraductal calculi.

Treatment

- As with chronic pancreatitis.
- High doses of insulin are often required with careful watch over hypoglycaemia.

Q. How will you differentiate tropical pancreatitis from alcoholic pancreatitis?

Features	Alcoholic pancreatitis	Tropical pancreatitis
• Age	35–45 years	20–40 years
• Sex	Males	Males > females
• Diabetes	Less common	More common
• Steatorrhoea	More common	Less common
• Intraductal calculi	Less common	Frequent
• Pancreatic malignancy	Less common	More common

Q. Discuss the differential diagnosis of sudden upper abdominal pain in a 40-year-old male.

- Peptic ulcer perforation
- Acute pancreatitis
- Acute mesenteric artery occlusion
- Aortic dissection or rupture
- Acute myocardial infarction
- Acute cholecystitis

Peptic Ulcer Perforation

- History of recurrent epigastric pain with relation to food and periodicity.
- Perforation results initially in severe epigastric pain, but it soon becomes generalised.
- Shoulder pain due to irritation of diaphragm.
- Abdominal examination reveals board-like rigidity, absent peristaltic sounds, and reduction or absence of liver dullness.
- Features of generalised peritonitis follow the initial phase of peritoneal irritation.
- Plain radiograph of abdomen in the erect posture may show gas under the diaphragm.

Acute Pancreatitis

- History of precipitating factors like alcohol, gallstones and pancreatic stones
- Acute severe pain in the epigastrium, usually 12–24 hours following heavy meal or alcohol
- Pain may radiate to the back
- Severe vomiting
- Examination reveals hypotension, tachycardia and epigastric tenderness
- Features of peritonitis
- Cullen's sign and Grey Turner's sign (uncommon)

- High serum amylase activity
- High serum lipase activity
- Plain radiograph of abdomen shows paralytic ileus or obstruction
- Chest radiograph might show left pleural effusion, collapse or consolidation of lung
- Ultrasonography and CT scan shows swollen, oedematous pancreas, stones and ascites

Mesenteric Artery Occlusion

- Previous history of recurrent abdominal pain after food (postprandial angina).
- Occlusion causes sudden onset of severe pain in the epigastrium and umbilical region.
- History of passing black stools.
- Clinical examination reveals signs of acute abdomen like guarding, rigidity, tenderness and paralytic ileus.
- Mesenteric arteriography confirms the diagnosis.

Aortic Dissection

- Sudden tearing pain radiating to the back.
- Evidence of associated diseases may be present.
  - Hypertension
  - Diabetes mellitus
  - Atherosclerosis
  - Aortic regurgitation
  - Marfan's syndrome
- Urine output may be decreased, if there is renal artery occlusion.
- Aortogram clinches the diagnosis.

Acute Myocardial Infarction

- Previous history of ischaemic heart disease (angina), hypertension, diabetes and other risk factors.
- Sudden onset of pain in the epigastrium, squeezing in type, associated with restlessness, pallor and profuse sweating.
- Clinical examination of cardiovascular system is usually normal.
- Occasionally, third heart sound and fourth heart sound are heard.
- A systolic murmur may be heard at the apex.
- ECG shows evidence of infarction.
- Cardiac injury enzymes (CK, troponin, AST and LDH) may be raised.

Acute Cholecystitis

- Pain in the right upper quadrant, epigastrium, right shoulder tip or interscapular region.
- Restlessness, pallor, sweating and vomiting.
- Clinical examination shows fever.
- Tenderness in the right hypochondrium and rigidity, worse on inspiration (Murphy's sign).
- Gallbladder may be palpable.
- Leucocytosis, jaundice and minor elevations of transaminases.
- Plain radiograph of abdomen may show gallstones (rare).
- Ultrasonography detects gall stones and gallbladder thickening.
- Cholescintigraphy shows cystic duct obstruction.

Chapter 9

Diseases of the Connective Tissues and Joints

Q. How do you classify polyarthritis? What are the causes of polyarthritis?

Classification and causes	
• Inflammatory	
• Infections	Acute bacterial arthritis, septicaemias, gonococcal arthritis, tuberculous arthritis, mycotic arthritis, syphilitic arthritis, viral arthritis, Lyme disease
• Immunologic	Rheumatoid arthritis (RA), rheumatic fever, seronegative spondyloarthritides, systemic lupus erythematosus (SLE), polymyositis, reactive arthritis, sarcoidosis
• Crystal induced	Gout, pseudogout (calcium pyrophosphate dihydrate deposition disease—CPPD), calcium hydroxyapatite deposition disease
• Reactive	Reiter's syndrome, Behcet's syndrome, sexually acquired reactive arthritis (SARA)
• Mechanical	Degenerative joint disease—osteoarthrosis
• Metabolic	Hypothyroidism, acromegaly, hyperparathyroidism, Cushing's disease, ochronosis, haemochromatosis, amyloidosis, Wilson's disease, hyperlipidaemia
• Neoplastic	Paraneoplastic arthropathies, carcinomatous arthropathy or neuromyopathy, hypertrophic osteoarthropathy (in some cases)
• Drug-induced	Thiazides causing gout, drug-induced lupus, corticosteroids
• Miscellaneous	Intestinal bypass arthritis, Whipple's disease

Q. Discuss the clinical manifestations, diagnosis and management of rheumatoid arthritis.

- RA is a chronic inflammatory joint disease with multisystem involvement.
- Females are affected three times more often than males (3:1).
- Onset is usually during fourth and fifth decades of life.
- Factors producing RA include infectious trigger, genetic predisposition and autoimmune response. The role of genetic influences in the aetiology of RA is marked by association with HLA-DR4 in 70% of patients.

Clinical Features

Onset

- Insidious onset with fatigue, anorexia, weakness and vague musculoskeletal symptoms.
- Acute onset with rapid development of polyarthritis accompanied by constitutional symptoms including fever, lymphadenopathy and splenomegaly.
- Palindromic onset where recurrent acute episodes of joint pain and stiffness occur in individual joints lasting only a few hours or days.

Articular Manifestations

- Joint involvement is usually symmetric. It is characterised by pain, swelling, tenderness and painful limitation of movements. The metacarpophalangeal and proximal interphalangeal joints of the hands, wrists, knees, and the metatarsophalangeal and proximal interphalangeal joints of the feet are the most common joints involved.
- Generalised stiffness may occur but "morning stiffness" lasting more than 1 hour is a characteristic feature. The intensity and duration of morning stiffness is a measure of disease activity. Some of these patients eventually develop a well-defined rheumatic disease, the most common being rheumatoid arthritis.

Hand and Wrist

- Swelling of the proximal, but not the distal interphalangeal joints results in "spindling" of the fingers.
- Hyperextension of the proximal interphalangeal joints with flexion of the distal interphalangeal joints results in "swan-neck" deformity.
- Flexion of the proximal interphalangeal joints and extension of the distal interphalangeal joints result in "boutonniere" or buttonhole deformity.
- Hyperextension of the first interphalangeal joint and flexion of the first metacarpophalangeal joint with a consequent loss of thumb mobility and pinch can occur.
- Extensor tendon rheumatoid granulomata and tendon rupture result in "dropped finger".
- Radial deviation of the wrist with ulnar deviation of the digits often with palmar subluxation of the proximal phalanges results in the "Z" deformity.
- Wrist synovitis with median nerve entrapment can result in carpal tunnel syndrome.
- Whole of hand may be swollen in very acute cases with pitting oedema over dorsum giving rise to the "boxing glove" appearance.

Foot and Ankle

- Swelling of the metatarsophalangeal joints results in "broadening" of the forefoot.
- Lateral deviation and dorsal subluxation of the toes.
- Plantar subluxation of the metatarsal heads.
- Eversion at the hindfoot (subtalar joint).
- Hallus valgus deformity.

Other Joints

- Flexion contractures of elbows, wrists, knees and hips.
- Shoulder joint involvement can occur as glenohumeral arthritis, rotator cuff fraying and rupture.
- Cervical spine involvement can result in atlanto-axial subluxation with progressive spastic quadriparesis.
- Cricoarytenoid joint involvement results in hoarseness of voice and stridor.
- Pain and swelling behind the knee can result from extension of inflamed synovium into the popliteal space (popliteal cyst or Baker's cyst).

Extra-Articular Manifestations

Rheumatoid Nodules

- These develop in 25% of persons with RA. They are firm, round masses felt in the subcutaneous tissues—e.g. the olecranon bursa, the proximal ulna, the Achilles tendon and the occiput. Visceral structures like heart, lungs and pleura may also be involved.
- Rheumatoid nodules are clinical predictors of more severe arthritis, seropositivity, joint erosions and rheumatoid vasculitis.

Rheumatoid vasculitis

- These manifestations are seen in patients with a high titre of circulating rheumatoid factor. Vasculitis results in the following manifestations:
  - Polyneuropathy and mononeuritis multiplex.
  - Cutaneous ulcerations, palpable purpurae and distal gangrene.
  - Visceral infarction resulting in stroke, acute myocardial infarction and mesenteric arteritis.

Pleuropulmonary Manifestations

- Pleural involvement results in effusion with low levels of pleural fluid glucose (less than 10 mg/dL).
- Pulmonary involvement resulting in interstitial fibrosis.
- Caplan's syndrome—multiple nodules and interstitial lung disease due to pneumoconiosis.

Cardiovascular Manifestations

- Pericarditis and chronic constrictive pericarditis.
- Premature atherosclerosis (an important cause of increased morbidity and mortality).
- Valvular involvement.
- Conduction defects.

Neurological Manifestations

- Nerve entrapment syndromes—e.g. carpal and tarsal tunnel syndromes.

- Spinal compression due to atlanto-axial subluxation.
- Peripheral neuropathies.

Ophthalmological Manifestations

- Scleritis, episcleritis and scleromalacia perforans.
- Sicca complex, comprising keratoconjunctivitis sicca, xerostomia and salivary gland enlargement.
- Glaucoma.

Felty's Syndrome

- This is the association of splenomegaly and neutropenia with RA.

Osteoporosis

- Osteoporosis secondary to rheumatoid involvement is very common. It may be aggravated by corticosteroid therapy and immobilisation.

Haematological Manifestations

- Normocytic normochromic anaemia.
- Thrombocytosis.
- Eosinophilia and mild leucocytosis.

Diagnosis

- Diagnosis of RA should be considered in patients with bilateral, symmetric, inflammatory polyarthritis involving small and large joints, with sparing of the axial skeleton except the cervical spine.
- The criteria for diagnosis are shown in the information box.

American College of Rheumatology/European League Against Rheumatism Classification Criteria for Rheumatoid Arthritis (2010)

Features	Score
A. Joint involvement*	
One large joint**	0
2–10 large joints	1
1–3 small joints*** (with or without involvement of large joints)	2
4–10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)****	5
B. Serology (at least one test result is needed for classification)	
Negative RF and negative anti-citrullinated protein antibodies (ACPA)	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
C. Acute-phase reactants (at least one test result is needed for classification)	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms	
<6 weeks	0
≥6 weeks	1

Add score of categories A–D; a score of ≥6/10 is needed for classification of a patient as having definite RA

Patients with a score of <6/10 are not classifiable as having RA, but their status can be re-assessed over time

*Joint involvement any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints and first metatarsophalangeal joints are excluded from assessment

**Large joints shoulders, elbows, hips, knees and ankles

***Small joints metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints and wrists

****Includes other joints not specifically listed (e.g. temporomandibular, acromioclavicular, sternoclavicular, etc.)

Investigations

- Markers of acute inflammation—raised ESR, anaemia, thrombocytosis, increased levels of acute phase proteins [e.g. C-reactive protein (CRP)] and increased plasma viscosity.
- Rheumatoid factor.
- Anti-citrullinated protein antibodies (ACPA), usually detected by anticyclic citrullinated peptide (CCP) antibodies.
- Radiographs of the affected joints may be useful. The characteristic radiological changes are symmetrical pattern of involvement, juxta-articular osteoporosis, soft tissue swelling, bone erosions and joint space narrowing.
- Ultrasonography and MRI have greater sensitivity than plain radiographs for the detection of soft tissue synovitis before joint damage.
- Rarely, synovial fluid analysis, synovial biopsy and arthroscopy are required. The synovial fluid contains 2000–50,000 leucocytes/μL with no crystals or organism.

Management

- Rest and splinting of the joints should be instituted in the acute stage of illness.
- Active and passive physiotherapy helps in mobilisation and prevention of contractures.

Analgesics

- Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first-line drugs used in the management of RA. They act by suppression of inflammation. None of the NSAIDs has been shown to be more effective than aspirin in the treatment of RA.

Disease Modifying Antirheumatic Drugs (DMARDs)

- Disease modifying antirheumatic drugs (DMARDs) are indicated in most cases. The traditionally used DMARDs are:
    - Hydroxychloroquine.
    - Oral gold (auranofin).
    - Parenteral (intramuscular) gold.
    - D-penicillamine.
    - Sulphasalazine.
    - Methotrexate.
    - Leflunomide.
- Most patients should be started on a combination of DMARDs and analgesics in the early course of disease.
- DMARDs reduce inflammation and prevent damage to joints, bones and ligaments.
- These agents take 3–4 months before their full effect.
- Biologicals are also DMARDs but are discussed below separately.

Methotrexate

- Currently, methotrexate is the drug of choice for RA. It may be given alone or in combination with hydroxychloroquine (hydroxychloroquine alone may not be effective in halting the progression of disease).
- The usual starting dose is 7.5–10 mg/week orally. If a positive response does not occur within 4–8 weeks, and there has been no toxicity, the dose should be increased by 2.5–5 mg/week each month to 20–25 mg/week before considering the treatment a failure.
- To improve the efficacy of MTX at dosages of 20–25 mg weekly, a change to subcutaneous administration should be considered.
- Folic acid is given in a dose of 5 mg once a week, on the day following methotrexate dose. It reduces some adverse events (gastrointestinal intolerance, stomatitis, hepatotoxicity, hyperhomocysteinaemia, and alopecia) associated with methotrexate.

Other DMARDs

- If the patient does not respond to methotrexate, the options include gold or D-penicillamine, sulphasalazine or leflunomide.
- A combination of methotrexate and leflunomide may be more effective than either drug alone.
- Leflunomide is a pyrimidine antagonist that blocks the enzyme dihydroorotate dehydrogenase, thereby blocking the synthesis of DNA. It has an efficacy similar to that of methotrexate. It can be used either alone or in combination with methotrexate. Dose is 10–20 mg/day.

Biological Response Modifiers (or Biologicals)

- Biological response modifiers are the agents that block specific immune factors leading to RA.
- These agents include tumour necrosis factor-α blockers, interleukin-1 receptor antagonists and anti-CD20 B cell agents.
- Anti-TNF-α inhibitors include monoclonal antibodies (infliximab, adalimumab, golimumab and certolizumab) and a soluble receptor fusion protein (etanercept).

- Other biologicals include rituximab (anti-CD20 antibody that blocks CD20 present on B cells), tocilizumab (a monoclonal antibody that binds to IL-6 receptors), abatacept (T-cell receptor CTLA4 that down regulates T cells) and anakinra (IL-1 receptor blocker).
- Usually given along with methotrexate or other conventional DMARDs.
- Infliximab.
  - A chimeric IgG1 monoclonal antibody (a chimera of human constant and mouse variable regions).
  - Binds to TNF-α and TNF-β and lyses TNF-producing cells to neutralise their activity.
  - Initial dose 3 mg/kg is given intravenously over 2 hours.
  - Same dose repeated at 2 and 6 weeks, and then every 8 weeks.
  - Dose can be increased to 10 mg/kg or infusion interval can be shortened, if an adequate response is not attained.
  - Patient monitored for any side effects during and 1 hour after infusion.
  - Side effects include pruritus, influenza-like symptoms, headache and hypotension. Occasionally, serum sickness can develop 1–2 weeks after infusion.
  - Reactivation of tuberculosis can occur. Other important side effects include soft tissue and joint infections, fungal infections and demyelination.
- Etanercept.
  - A soluble dimeric fusion protein consisting of soluble human p75-TNF receptor and Fc portion of human IgG1.
  - It blocks the TNF receptor.
  - Dose is 25 mg subcutaneously twice a week.
  - Injection site reactions in the form of redness and swelling can occur.
- Adalimumab
  - A humanised IgG1 monoclonal antibody (fully human constant and variable regions).

Immunosuppressants

- Immunosuppressants are used as third-line drugs for disease that recurs or does not respond to second-line agents. They inhibit the immune system and have potentially serious side effects. These include cyclophosphamide and azathioprine. However, in acute vasculitis causing serious organ involvement intravenous cyclophosphamide may be lifesaving.

Corticosteroids

- Corticosteroid therapy is reserved for selected indications. Intra-articular corticosteroid injections are useful in the acute stage. Prednisolone is administered orally. The indications of systemic corticosteroid therapy are:
  - Active synovitis in many joints, in spite of good conservative regimen of antirheumatic therapy and physiotherapy. In such cases, low-dose glucocorticoids should be considered in addition to DMARDs.
  - Incapacitating constitutional symptoms such as fever and weight loss, neuropathy and rheumatoid vasculitis.

Surgical Therapy

- Surgical therapy is useful in maintenance of joint function, and prevention and correction of deformities. Various modalities include reconstructive hand surgery, arthroplasties, total joint replacements, tenosynovectomy and open or close synovectomy.

Q. Explain rheumatoid factor.

- Rheumatoid factors (RFs) are IgM and IgG autoantibodies against the Fc portion of IgG. In clinical practice, IgM rheumatoid factor is widely used.
- RF is present in about 80% of patients with RA. It can also be present in a number of other conditions.

Conditions Associated with a Positive Rheumatoid Factor

Rheumatic conditions (prevalence)	Other conditions
RA (80%)	Age >60 years
Sjogren's syndrome (75–95%)	Infections (endocarditis, tuberculosis, syphilis, mumps)
Systemic lupus erythematosus (SLE) (15–30%)	Chronic liver disease
Systemic sclerosis (20–30%)	Sarcoidosis
Cryoglobulinaemia (40–90%)	Interstitial lung disease
Mixed connective tissue disease (CTD) (50–60%)	Primary biliary cirrhosis

- RF testing is appropriate in patients suspected of having RA. If clinical suspicion is low, RF testing is unlikely to be helpful. RF is also a good screening tool, when Sjogren's syndrome or cryoglobulinaemia is suspected.
- In patients with RA, RF titres generally correlate with extra-articular manifestations and disease severity. However, RF titres are not useful in following disease progression. Hence, if a patient is RF-positive, there is no need to repeat it later.

Q. What are anti-citrullinated protein antibody? Explain.

Q. Write a short note on anticyclic citrullinated peptide (CCP) antibody.

- Autoantibodies seen in patients with RA.
- Anti-citrullinated protein antibodies (ACPA) recognise citrulline-containing peptides/proteins as common antigenic entity.
- Citrulline is a non-standard amino acid generated by post-translational modification of arginine during a variety of biological processes, which include inflammation. Some of the citrullinated proteins include filaggrin, fibrin, fibrinogen, vimentin, types I and II collagens and modified cyclic citrullinated peptides.
- IgG CCP is a type of ACPA, where antibody is directed against the antikeratin epitope that contains citrulline.
- Citrullinated extracellular fibrin is found within the synovium of patients with RA.
- Highly specific (97%) but less sensitive (50%) for diagnosis of RA.
- It is more likely to be present early in the course of the disease and may be helpful in confirming the serological diagnosis in patients with a negative or equivocal rheumatoid factor.
- Presence of anti-CCP antibody may be a marker for the development of more severe erosive disease. Thus anti-CCP positive patients may require an aggressive treatment.

Q. Discuss COX enzymes and COX-2 inhibitors.

- NSAIDs exert their anti-inflammatory effects through the inhibition of prostaglandin synthesis from arachidonic acid by blocking cyclooxygenase (COX) enzyme.
- There are two isoforms of COX: COX-1 and COX-2.
  - COX-1 enzyme is constitutively expressed in gastrointestinal tract, kidneys and platelets. It is responsible for the production of thromboxane A_2 and prostaglandins. Under the influence of COX-1, prostaglandins maintain integrity of the gastric mucosa, mediate platelet function and regulate renal blood flow. Thromboxane A_2 is a vasoconstrictor and potent stimulator of platelet aggregation.
    - COX-2 is primarily induced at the site of inflammation, producing prostaglandins that mediate inflammation and pain. Prostaglandin I_2 a potent vasodilator and inhibitor of platelet function is predominantly regulated by the COX-2 isoform.
- Conventional NSAIDs inhibit both the isoforms of COX in varying degrees.
- Inhibition of COX-1 is necessary for anti-inflammatory and analgesic effects, but may account for adverse effects associated with traditional NSAIDs.
- COX-2 (cyclooxygenase-2) inhibitors are NSAIDs that play a major role in the management of inflammation and pain caused by arthritis. These agents selectively inhibit the cyclooxygenase-2 enzyme and have minimal antiplatelet effects because they do not affect the thromboxane A_2 pathway.
- With respect to their analgesic and anti-inflammatory properties there is no significant difference among various traditional NSAIDs and COX-2 inhibitors.
- These agents have relatively lesser gastrointestinal side effects (including lower incidence of peptic ulcer) compared to the conventional and non-selective NSAIDs.
- These agents do not have significant effect on platelets.
- Selective COX-2 inhibitors appear to have little risk of precipitating bronchospasm in patients with aspirin-induced asthma.
- Like traditional NSAIDs, COX-2 inhibitors can produce significant changes in renal functions, and hence, should be cautiously used in patients with diabetes, dehydration and congestive heart failure.
- This class of drugs includes celecoxib, rofecoxib, valdecoxib, etoricoxib and etodolac.
- Unfortunately, trials indicated a higher risk of myocardial infarction, heart failure and stroke (thromboembolic complications) in patients using COX-2 inhibitors compared to those taking other NSAIDs. Hence, presently, two COX-2 inhibitors (rofecoxib and valdecoxib) have been withdrawn. Celecoxib, etodolac and etoricoxib are available for clinical use.
- A possible explanation for a prothrombotic state induced with these agents is that they inhibit the vasodilating effects of endothelial prostaglandin I_2 without affecting thromboxane A_2 (a product of platelet COX-1 activity) resulting in an unbalanced prothrombotic state in patients at risk.

Q. What is Felty's syndrome? Enumerate the clinical manifestations and laboratory abnormalities of Felty's syndrome.

- Felty's syndrome refers to the constellation of neutropenia, splenomegaly and RA. It is considered an extra-articular manifestation of RA.
- It is seen in patients with long-standing, chronic, seropositive RA.
- It has a poor prognosis, with an increased mortality due to a higher incidence of severe infection.

Clinical Features (In Addition to Features of RA)

- Most often, rheumatoid arthritis is present for several years before neutropenia and splenomegaly become apparent.
- Splenomegaly.
- Lymphadenopathy.
- Skin pigmentation.
- Weight loss.
- Keratoconjunctivitis sicca.
- Subcutaneous rheumatoid nodules.
- Vasculitis resulting in mononeuritis multiplex and necrotising skin lesions.
- Recurrent infections and chronic leg ulcers.
- Carpal tunnel syndrome.
- Greater risk of developing non-Hodgkin's lymphoma.

Laboratory Abnormalities

- Neutropenia <1500/mm^3, anaemia and thrombocytopenia.
- High titres of rheumatoid factor.
- Increased levels of circulating immune complexes (CIC).

Treatment

- Treatment of underlying RA.
- Immunosuppressive agents particularly methotrexate and azathioprine are beneficial.
- In patients with life-threatening or refractory bacterial infection, G-CSF may be given to rapidly reverse neutropenia.
- Splenectomy is indicated in:
  - Recurrent or serious infections.
  - Severe ulcers.
  - Severe and persistent granulocytopenia (<500 mm^3), despite DMARD therapy for rheumatoid arthritis.
  - Severe anaemia due to hypersplenism.
  - Thrombocytopenia haemorrhage due to hypersplenism.

Q. What is Still's disease?

- Still's disease is systemic-onset, seronegative RA [juvenile idiopathic arthritis (JIA)] occurring in children.
- Characteristically, the disease presents with high fever, arthralgia and arthritis, myalgia and also hepatosplenomegaly, lymphadenopathy, evanescent skin rashes, anaemia and leucocytosis. Pleurisy and pericarditis may occur.
- Approximately, 10% of children develop overt clinical features of macrophage activation syndrome, a life-threatening condition characterised by fever, organomegaly, cytopenia, hyperferritinemia, hypertriglyceridemia, hypofibrinogen-emia and coagulopathy, The diagnostic hallmark is the presence on bone marrow examination of numerous, well-differentiated macrophages that are engaged actively in the phagocytosis of haematopoietic elements.
- Tests for rheumatoid factor are negative, but there is neutrophilia, thrombocytosis and elevated ESR.
- The disease has a good prognosis and most of the patients respond to NSAIDs or steroids.

Q. Describe adult onset Still's disease.

- It is a form of Still's disease that occurs in adults and is characterised by a triad of highspiking fever, a characteristic evanescent skin rash and arthritis/arthralgias.
- Fever is transient, lasting typically under 4 hours and is most commonly quotidian or double quotidian in pattern.
- Rash is maculopapular, predominantly found on the proximal limbs and trunk.
- Joints affected most frequently are the knees, wrists and ankles.
- Other manifestations include lymphadenopathy, hepatomegaly, splenomegaly, pleuritis and pericarditis.

- Macrophage activation syndrome can occur in some patients.
- Investigations show anaemia, neutrophilic leucocytosis, thrombocytosis, raised ESR and CRP elevated liver enzymes.
- Ferritin levels usually higher than those found in patients with other autoimmune or inflammatory diseases. A more useful marker is reduced level (<20%) of glycosylated fraction of ferritin.
- Course.
  - Self-limited or monocyclic pattern characterised by remission within 1 year from the onset.
  - Intermittent or polycyclic systemic pattern recurrent flares, with or without articular symptomatology.
  - Chronic articular pattern dominant articular manifestations that can lead to joint destruction.
- Treatment is with NSAIDs and steroids. Role of DMARDs (biological and non-biological) is not clear but may be used in refractory cases.

Q. Discuss briefly juvenile idiopathic arthritis (JIA) or juvenile rheumatoid arthritis (JRA) or juvenile chronic arthritis (JCA) and its treatment.

- Criteria for diagnosis of JIA include age of onset less than 16 years, disease duration greater than 6 weeks, arthritis and exclusion of other forms of juvenile arthritis.
- The terms juvenile rheumatoid arthritis (JRA) and juvenile chronic arthritis (JCA) are not used at present.
- Juvenile idiopathic arthritis is subdivided into following types:
  - Polyarticular juvenile idiopathic arthritis affects more than four joints and is more common in young females than young males. Symptoms include swelling or pain in five or more joints. The small joints of the hands are affected as well as the weight-bearing joints such as the knees, hips, ankles, feet and neck. In addition, the child may have low-grade fever and nodules over bony prominence. Based on the presence or absence of rheumatoid factor, it is termed as polyarticular JIA, RF⁺ or polyarticular JIA, RF⁻.
  - Oligoarticular or pauciarticular JIA affects fewer than five joints. Symptoms include pain, stiffness or swelling of affected joints. Knee and wrist joints are the most commonly affected. Eye involvement in the form of iridocyclitis can occur. These patients are more often antinuclear antibodies (ANA) positive compared to other categories.
  - Still's disease or systemic juvenile idiopathic arthritis presents with skin rash and fever in addition to arthritis. It may involve internal organs (e.g. splenomegaly, hepatomegaly, pericarditis, pleural effusion, etc.).
  - Enthesitis-related juvenile idiopathic arthritis presents with asymmetric joint involvement of lower limbs with enthesitis (tenderness at the insertion of a tendon, ligament, joint capsule or fascia to the bone). Sacroiliitis with pain is often present. Eye involvement can occur. HLA-B27 is positive in majority. History of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease or acute anterior uveitis in a first-degree relative often present.
  - Psoriatic juvenile idiopathic arthritis presents with symmetrical or asymmetrical arthritis and psoriasis or arthritis along with dactylitis, nail pitting, onycholysis or psoriasis in a first-degree relative.

Treatment

- For oligoarticular JIA, intra-articular injections of steroids and appropriate use of NSAIDs are the mainstay of treatment. Disease modifying antirheumatic drugs (DMARDs) are generally not recommended for this group, although occasionally, methotrexate may be difficult to control uveitis or when damage to a critical joint threatens function (e.g. wrist and hip).
- For polyarticular JIA treatment is similar to that for RA.
- For systemic JIA, NSAIDs and corticosteroids. Methotrexate is not very effective. Biologic agents which inhibit IL-1 (anakinra) or IL-6 (tocilizumab) are recommended as glucocorticoid-sparing therapies.

Q. What are the pleuropulmonary manifestations of rheumatoid arthritis?

- Pleuropulmonary manifestations of rheumatoid arthritis are the extra-articular features. These include the following entities:
  - Pleural effusion with a characteristically low pleural fluid glucose level (<10 mg/dL).
  - Interstitial lung disease—fibrosing alveolitis.
  - Rheumatoid nodules manifesting as solitary pulmonary nodules.
  - Cavitated rheumatoid nodules.
  - Bronchiolitis obliterans organising pneumonia.
  - Granulomatous pneumonitis.
  - Pulmonary arteritis (vasculitis) resulting in infarction.

- Caplan's syndrome is the coexistence of seropositive RA and rounded fibrotic peripherally located pulmonary nodules of 0.5–5 cm diameter in patients with coal worker's pneumoconiosis (CWP).

Q. Discuss the classification, clinical manifestations, diagnosis and management of Sjogren's syndrome.

Q. Describe keratoconjunctivitis sicca.

- Sjogren's syndrome is an immunologic disorder characterised by progressive destruction of exocrine glands leading to mucosal and conjunctival dryness. A diagnosis of Sjogren's syndrome is made, when there is a triad of keratoconjunctivitis sicca, xerostomia and mononuclear cell infiltration of salivary gland.

Classification and types	
• Primary (sicca syndrome)	The disease occurs by itself, in the absence of any connective tissue disorder
• Secondary	The disease is accompanied by a variety of autoimmune disorders. These include RA, SLE, progressive systemic sclerosis, primary biliary cirrhosis, chronic active hepatitis, myasthenia gravis, polymyositis and thyroiditis
• Glandular type	The only clinical manifestations are within the exocrine system
• Extraglandular type	Other tissues are also involved

Incidence

- The disease occurs in third to fourth decades and predominantly affects females.
- The two main mechanisms of tissue destruction in Sjogren's syndrome are lymphocytic infiltration and immune-complex deposition.

Clinical Features

- Xerophthalmia encompasses itching and grittiness, and may be associated with soreness, photosensitivity, ocular fatigue, and reduced visual acuity. Diminished tear secretion may lead to chronic irritation and destruction of conjunctival epithelia (keratoconjunctivitis sicca). Complications include corneal ulceration and infection of the eyelids.
- Xerostomia is dryness of mouth resulting from lack of salivary secretion. This leads to increased local bacterial, fungal infections, and dental caries.
- Enlargement of the parotid or other major salivary glands occurs in 65% of patients with primary Sjogren's syndrome, but is uncommon in secondary Sjogren's syndrome.
- Fatigue is common and seen in 70% cases.
- Renal involvement in the form of interstitial nephritis or glomerulonephritis. Interstitial nephritis may lead to renal tubular acidosis (both type 1 and 2).
- Arthralgias are commonly seen while typical nonerosive arthritis is less frequent.
- Cutaneous and systemic vasculitis.
- Nasal crusting, epistaxis, recurrent sinusitis, dry cough and dyspnoea occur due to dry nose, dry trachea, small airway obstruction and/or interstitial lung disease.
- Polyneuropathies or mononeuritis are multiplex.
- Approximately, 10% of these patients develop a lymphoproliferative process that may go on to develop a non-Hodgkin's lymphoma. Salivary glands are the most common site of involvement. Persistent parotid gland enlargement, lymphadenopathy, lymphopenia and cryoglobulinaemia are manifestations suggesting the development of lymphoma.
- Hashimoto's thyroiditis is a common accompaniment of Sjogren's syndrome.

Laboratory Investigations

- Common laboratory abnormalities are raised ESR, leucopenia, thrombocytosis, elevated levels of CIC and autoantibodies [antibodies to Ro/SSA or La/SSB, ANA or RF).
- Schirmer's test is positive. Rose Bengal test evaluates corneal epithelium.
- Measurement of salivary flow is done by salivary sialometry. Salivary gland involvement may be tested by salivary scintigraphy.
- Histopathology of minor salivary glands.

Treatment

- Ocular and mucosal lubricants like artificial tears, ophthalmologic lubricating ointments, lubricating agents for dryness of mouth, nasal sprays of normal saline and moisturising skin lotions.
- Cyclosporin emulsion has been found to be useful in ocular dryness.
- Muscarinic agonists (pilocarpine and cevimeline) have been approved for the treatment of the sicca symptoms. These agents stimulate the M1 and M3 receptors present on salivary glands and tear glands leading to increased secretory function.
- Hydroxychloroquine is helpful for arthralgias.
- Corticosteroids are useful, particularly in the management of glomerulonephritis and pneumonitis.
- Immunosuppressive therapy (cyclosporin A, azathioprine, methotrexate and mycophenolic acid) is indicated for systemic vasculitis.
- Biological agents, including infliximab, interferon-α and anti-CD20 antibodies (rituximab) are being increasingly used in the treatment of Sjogren's syndrome.

Q. What are spondyloarthropathies?

Q. What are seronegative spondyloarthropathies (SSA)?

- Also known as spondyloarthritides.
- Diverse group of inflammatory arthritides that share genetic predisposing factors and clinical features (inflammatory back pain due to sacroiliitis and spondylitis, peripheral arthritis, enthesitis—inflammation at sites where tendons, ligaments or joint capsules attach to bone, dactylitis and acute anterior uveitis).

Clinical Criteria for Inflammatory Back Pain

- Onset before age of 45 years
- Insidious onset
- Improvement with exercise
- Morning stiffness
- Persistence (for at least 3 months)

Note: Coexistence of four out of five criteria allows the definition of inflammatory back pain

- Sometimes, spinal and sacroiliac joint involvement may not occur and patient presents with peripheral, asymmetrical arthritis, generally in the lower limbs.
- Associated with HLA-B27.
- RF negative; therefore, known as "seronegative".
- Include ankylosing spondylitis, reactive arthritis (including Reiter's syndrome), psoriatic arthritis, inflammatory bowel disease–associated spondyloarthropathy and undifferentiated spondyloarthropathy.
- No specific diagnostic tests.
    - Raised ESR, CRP, and anaemia.
    - Sacroiliitis or spondylitis on radiographs.
    - MRI more sensitive in diagnosing early sacroiliitis.

Features

- Inflammatory spinal pain or synovitis predominantly involving lower limbs in an asymmetric fashion with one or more of the following:
    - Radiographic sacroiliitis with or without accompanying spondylitis
    - Enthesitis and dactylitis
    - Association with chronic inflammatory bowel disease
    - Association with psoriasis and other mucocutaneous lesions
    - Urethritis or cervicitis or acute diarrhoea occurring within 1 month before arthritis
    - Tendency for anterior ocular inflammation
    - Increased familial incidence
    - Occasional aortitis and heart block
    - No association with rheumatoid factor
    - Strong association with HLA-B27

Q. Explain ankylosing spondylitis, rheumatoid spondylitis or Marie–Strumpell disease.

- Ankylosing spondylitis is a seronegative chronic inflammatory arthritis that primarily affects the axial skeleton with a predilection for lumbar spine and sacroiliac joints.
- 90% of the affected people carry the histocompatibility antigen HLA-B27.
- It is also associated with inflammatory bowel disease.
- The disease usually occurs in the second and third decades with a male to female ratio of 4:1.

Clinical Features

- Involvement of the lumbar spine results in low back pain with nocturnal exacerbations. Characteristically, this is associated with low back morning stiffness that improves with activity. Low-back stiffness may be precipitated by inactivity. Early physical signs include failure to obliterate the lumbar lordosis on forward flexion and restriction of the movements of lumbar spine in all directions. The limitation of forward flexion of lumbar spine can be measured by the Schober test:
  - Mark points on the spine 5 cm below and 10 cm above the posterior superior iliac spines.
  - Ask the patient to bend forward maximally.
  - The distance between the two marks should increase by 5 cm or more in normal persons. An increase of less than 5 cm suggests decreased range of motion of the lumbar spine.
- Involvement of the sacroiliac joints causes low back pain. Pain in the sacroiliac joints may be elicited either by direct pressure or by manoeuvres that stress the joint—e.g. "figure of 4 test" (Patrick's test).
  - One limb is guided into "figure of 4" position with the ipsilateral ankle resting across the contralateral thigh.
  - The ipsilateral knee is then pressed downwards with one hand, while providing counterpressure with the other hand on the contralateral anterior superior iliac spine.
  - This manoeuvre tends to stress the sacroiliac joint on the side being tested.
- Enthesitis is common. Inflammation at the Achilles tendon and plantar fascia calcaneal insertions is particularly common, and manifests as heel pain. Like arthritis, enthesitis typically is aggravated by rest and improved with activity. Other areas of enthesitis include superior and inferior aspects of patella, metatarsal heads and spinal ligament insertions on vertebral bodies.
- Involvement of the thoracic spine, costovertebral joints and costosternal joints result in chest pain, diminished chest expansion (<5 cm) and thoracic kyphosis.
- Involvement of the cervical spine results in neck pain and a forward stoop of the neck.
- Peripheral arthritis is usually late and asymmetric. Involvement of hips and shoulders result in pain and limitation of movement. Hip involvement may lead to flexion contractures, compensated by flexion at knees.

Extra-Articular Manifestations

• Acute anterior uveitis	• Osteoporosis
• Iritis	• Myelopathy secondary to atlanto-axial subluxation
• Aortic regurgitation and heart failure	and spinal fracture
• Conduction defects	• Cauda equina syndrome
• Apical pulmonary fibrosis and cavitation	• Amyloidosis

Investigations

- Erythrocyte sedimentation rate (ESR) is raised. Tests for rheumatoid factor (RF) are negative.
- HLA-B27 is present in >90% cases.
- MRI and bone scan can pick up early sacroiliitis.
- Ultrasonography can be useful in detecting enthesitis.

Radiological Manifestations

• Blurring of sacroiliac joint margins followed by erosions and sclerosis
• Erosion and sclerosis at the anterior corners of vertebrae
• Syndesmophyte (ossification of annulus fibrosus) formation, marginal
• "Squaring" of lumbar vertebrae (due to enthesitis involving spine)
• Bamboo spine (multiple syndesmophytes bridging the intervertebral spaces)
• Diffuse osteoporosis of spine
• Atlanto-axial subluxation and vertebral fractures
• Erosive changes in symphysis pubis, ischial tuberosities and peripheral joints

Diagnostic Criteria

Modified New York Criteria (1984)

Radiological criteria

- Sacroiliitis, grade ≥II bilaterally
  OR
- Sacroiliitis, from grades III to IV unilaterally

Clinical criteria (two of the following three)

- Low back pain and stiffness for more than 3 months that improves with exercise but is not relieved by rest
- Limitation of motion of the lumbar spine in both the sagittal and frontal planes
- Limitation of chest expansion relative to normal values correlated for age and sex

Grade II—sclerosis with some erosions; Grade III—severe erosions, partial ankylosis. Grade IV—complete ankylosis.

Management

- Regular exercises, active and passive physiotherapy.
- Symptomatic relief can be obtained with NSAIDs. Indomethacin is the most effective drug. It may be given up to a maximum daily dose of 100 mg.
- Sulphasalazine and methotrexate are useful to control peripheral joint symptoms but not for axial symptoms.
- Local corticosteroid injections and rarely systemic corticosteroids may be necessary.

Anti-TNF-α agents

- Infliximab, etanercept, golimumab and adalimumab are options for the treatment of patients with active ankylosing spondylitis who are not satisfactorily responded to NSAIDs. Duration of treatment is 2–3 years. These agents are useful for axial joint involvement not responding to adequate doses of NSAIDs given for 3 months. Also useful in peripheral arthritis not responding to sulphasalazine for 4 months.
  - Infliximab—5 mg/kg intravenously every 6–8 weeks.
  - Etanercept—25 mg subcutaneously twice a week initially.
  - Both these agents are also approved for RA, psoriasis, psoriatic arthritis and JIA.
  - In addition, infliximab also approved for Crohn's disease.
  - Contraindicated in pregnant patients, patients with active infection, SLE or multiple sclerosis.
  - Monitor patient for development of tuberculosis.

Others

- Reconstructive surgery.
- Control of uveitis by local steroid drugs.

Q. Write a short note on Reiter's syndrome.

Q. Discuss the clinical features, diagnosis and management of reactive arthritis.

- Classical Reiter's syndrome is a triad of non-specific urethritis in males or cervicitis in females, conjunctivitis and arthritis 2–4 weeks following enteric or urogenital infections.
- The term "reactive arthritis" includes all cases of spondyloarthropathy who have classical features of Reiter's syndrome with or without evidence of antecedent infection.
- The term Reiter's syndrome is restricted to those cases that have classical features along with evidence of antecedent infection and is a part of reactive arthritis.
- Poncet's disease is a reactive arthritis to tuberculous infection. Resolution of arthritis upon starting of adequate anti-tuberculous therapy is mostly within a few weeks. Chronic arthritis does not occur.
- More than 75% of the patients have the histocompatibility antigen HLA-B27.
- Common enteric pathogens triggering the disease are *Shigella*, *Salmonella*, *Yersinia* and *Campylobacter* species, and *Clostridium difficile*.
- Common urogenital pathogens are *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Streptococcus pyogenes*.

- However, a similar spectrum of clinical manifestations can occur after infection with other organisms at other sites also.
- Patients with clinical features of reactive arthritis who lack both evidence of an antecedent infection and the classic features of Reiter's syndrome (urethritis, arthritis and conjunctivitis) are classified as undifferentiated spondyloarthropathy.
- The clinical symptoms of reactive arthritis usually develop with a delay of 1–3 weeks after onset of infection.
- Onset of arthritis is typically acute particularly affecting joints of lower limbs in an asymmetrical fashion. Arthritis is generally oligoarticular with <5 joints involvement.
- Enthesitis and dactylitis (inflammation of entire digit) are very common.
- Keratoderma blennorrhagica—hyperkeratotic lesions on the palms of the hands or the soles of the feet. Seen in Reiter's syndrome.
- Circinate balanitis—a painless erythematous lesion of the glans penis.
- Usually a self-limiting course of 3–12 months.
- Up to 50% of patients have recurrent bouts of arthritis and 15–30% develop chronic arthritis or sacroiliitis.

Clinical Features

Constitutional	Fatigue, malaise, fever, weight loss
Musculoskeletal	Arthritis (particularly affecting joints of the lower limbs), dactylitis or "sausage digit" (diffuse swelling of a finger), Achilles tendonitis, plantar fasciitis
Urogenital	Urethritis, acute haemorrhagic cystitis, prostatitis, cervicitis, salpingitis
Ocular	Conjunctivitis, anterior uveitis, acute iritis
Mucocutaneous	Keratoderma blennorrhagica, circinate balanitis, nail dystrophy, heaped-up hyperkeratosis
Others	Aortic regurgitation, conduction defects, central or peripheral nervous system involvement, pericarditis, pleurisy

Investigations

- Raised erythrocyte sedimentation rate (ESR).
- Anaemia and polymorphonuclear leucocytosis.
- Characteristic synovial fluid findings (more than 2000 white blood cells/mL with a predominance of neutrophils).
- HLA-B27 is positive in more than 75% of cases.
- Serum tests for rheumatoid factor and antinuclear antibodies are negative.

Radiological Features

- Juxta-articular osteoporosis.
- Erosive changes and reduction in joint space.
- Periostitis with reactive new bone formation due to enthesitis.
- Spurs at the insertion of the plantar fascia.
- Sacroiliitis (less common than ankylosing spondylitis).
- Discontinuous spondylitis with non-marginal syndesmophytes.

Management

- Rest and NSAIDs.
- Intra-articular or local steroid injections and rarely systemic steroids.
- Non-specific urethritis is treated with a short course of tetracycline or ciprofloxacin. In patients with acute Chlamydia-induced reactive arthritis, a prolonged course of antibiotics (from 4 to 12 weeks), either tetracycline or ciprofloxacin, should be given.
- No role of antibiotics in reactive spondyloarthropathy secondary to enteric infections.
- Sulphasalazine, azathioprine and methotrexate may be useful in patients with persistent symptoms.
- Biologicals like infliximab, etanercept, adalimumab and thalidomide in refractory cases.

Q. What are the types of psoriatic arthritis? Discuss briefly the clinical manifestations, diagnosis and management of psoriatic arthritis.

- Psoriatic arthritis is a seronegative arthritis found in patients with psoriasis, a past or family history of psoriasis or with characteristic nail changes.
- Occurs in about 20% of patients of psoriasis.

Types

• Symmetric psoriatic arthritis	• Psoriatic spondylitis
• Asymmetric psoriatic arthritis	• Predominant distal interphalangeal arthritis
• Arthritis mutilans	

Clinical Features

- The most common form (asymmetric arthritis) is characterised by frequent involvement of proximal and distal interphalangeal joints with characteristic "sausage-shaped" digits (dactylitis inflammatory involvement of tendons and tendon sheaths leading to inflammatory swelling of affected fingers or toes). Usually, less than four joints are involved.
- Symmetric arthritis affects joints on both sides simultaneously and presents like RA.
- Spondylitis form is characterised by stiffness of the lower spine or cervical spine. Joints of hands and feet can also be affected. Sacroiliitis, often asymmetrical, occurs in about 40%.
- Distal interphalangeal predominant type of psoriatic arthritis is characterised by inflammation and stiffness of distal interphalangeal joints of hands and feet. Nail changes are often marked in this type of arthritis.
- Arthritis mutilans is a severe, deforming and destructive arthritis that can progress over months or years causing severe joint damage.
- Enthesitis is common.
- Characteristic skin lesions of psoriasis may be present. These are widespread scaling silvery lesions, seen typically over extensor surfaces, scalp, ears and perineum. In the majority of cases, skin manifestations precede joint involvement, although the reverse occurs in 15–20% of cases.
- Characteristic nail changes of psoriasis are pitting, onycholysis, subungual hyperkeratosis and horizontal ridging. These are present in nearly 80% patients with arthritis.
- Uveitis, unilateral or bilateral and generally chronic.

Diagnosis

- Raised ESR and negative tests for rheumatoid factor and antinuclear antibodies.
- Radiological findings are similar to those of RA, but osteoporosis is relatively less common. Radiographs of distal interphalangeal joints may show pencil-in-cup changes because of marked resorption of bone. Other findings include enthesitis with periosteal reaction, sacroiliitis and spondylitis.

Psoriatic Arthritis versus RA

- Clinical features are important to differentiate seronegative (rheumatoid factor-negative), rheumatoid arthritis (RA) with coincidental psoriasis from patients with peripheral psoriatic arthritis. Important features favouring diagnosis of psoriatic arthritis include the following:
  - Presence of nail psoriasis.
  - Absence of features characteristic of RA (e.g. rheumatoid nodules, extra-articular involvement and high titres of rheumatoid factor).
  - Involved joints are usually less tender and swollen, and less symmetric in distribution than in RA.
  - Dactylitis, enthesitis and distal interphalangeal joint involvement are common.

Management

- Majority of the patients respond to NSAIDs.
- Other modalities of treatment include gold therapy, sulphasalazine, methotrexate, cyclosporin, photochemotherapy and intra-articular steroid injections.
- Anti-TNF-α agents (infliximab, etanercept and adalimumab) in severe cases.

Q. Discuss briefly about spondyloarthropathy associated with inflammatory bowel disease.

- Also known as enteropathic spondyloarthropathy.
- Occurs in about 20% of patients, who have inflammatory bowel disease (IBD).
- Occurs more often in patients with Crohn's disease than in those with ulcerative colitis.
- May manifest before clinically apparent bowel disease.

Clinical Features

Peripheral Arthritis

- Type 1 involves less than five joints and is clinically characterised by acute self-limiting attacks of less than 10 weeks duration, often paralleling intestinal inflammatory activity. Moreover, it is strongly associated with other extraintestinal manifestations of IBD such as erythema nodosum.
- Type 2 is polyarticular, involving five or more joints with symptoms that persist for months and years running independently from IBD flares. This type is associated with uveitis, but not with other extraintestinal manifestations.
- Both types are usually nonerosive and nondeforming, but may become chronic and erosive in 10% of patients.
- No significant association between peripheral arthropathies and HLA-B27 in IBD.

Inflammatory Back Pain

- Insidious in onset, frequently unilateral and intermittent at onset, more intense at rest, associated with stiffness but relieved by movement, exacerbated by cough or sneezing, and accompanied by fatigue.
- May manifest as spondylitis indistinguishable from ankylosing spondylitis.
- Axial disease (spondylitis disease) is generally independent of IBD activity.
- May be associated with peripheral arthritis
- Strongly associated with HLA-B27.

Others

- Enthesitis.
- Dactylitis.
- Uveitis
- Extra-articular manifestations of IBD.

Treatment

- NSAIDs to be used cautiously because they can exacerbate IBD.
- Sulphasalazine effective in the treatment of IBD and arthritis.
- Azathioprine and methotrexate may also be useful.
- Anti-TNF-α inhibitors beneficial in axial involvement.

Q. Describe undifferentiated spondyloarthropathy.

- This entity indicates involvement of spine and joints producing typical features of spondyloarthropathy but without any criteria for any of the well defined spondyloarthropathies (discussed above).
- Over time, a small proportion of these patients develop a well defined spondyloarthropathy.
- Clinical features include inflammatory back pain, unilateral or alternating buttock pain, enthesitis, dactylitis and occasionally extra-articular manifestations.
- Generally good prognosis with good response to NSAIDs.

Q. How will you differentiate various spondyloarthropathies?

Feature	Ankylosing spondylitis	Reactive arthritis	Psoriatic arthritis	IBD-associated spondyloarthropathies
• Age at onset	Late teens to early adulthood	Late teens to early adulthood	35–45 years	Any age
• Male to female ratio	4:1	5:1	1:1	1:1

Feature	Ankylosing spondylitis	Reactive arthritis	Psoriatic arthritis	IBD-associated spondyloarthropathies
• HLA-B27 positive	90%	80%	40%	30%
• Frequency of sacroiliitis	100%	40–60%	40%	20%
• Distribution of sacroiliitis	Symmetrical	Asymmetrical	Asymmetrical	Symmetrical
• Syndesmophytes	Marginal	Non-marginal	Non-marginal	Marginal
• Enthesitis	Common	Very common	Very common	Occasional
• Dactylitis	Uncommon	Common	Common	Uncommon
• Skin changes	None	Circinate balanitis, keratoderma blennorrhagica	Psoriatic lesions	Erythema nodosum, pyoderma gangrenosum
• Nail changes	None	Onycholysis	Pitting, onycholysis	Clubbing
• Uveitis	Acute	Acute	Chronic	Chronic
• Pulmonary involvement	Upper lobe fibrosis	None	None	None
• GI involvement	None	Diarrhoea	None	Features of associated Crohn's disease or ulcerative colitis
• Genitourinary involvement	None	Urethritis, cervicitis	None	None
• Cardiac involvement	Aortic regurgitation, conduction defects	Aortic regurgitation, conduction defects	Aortic regurgitation, conduction defects	Aortic regurgitation

Q. Discuss briefly symptoms, diagnosis and treatment of Behcet's disease.

- Behcet's disease is characterised by recurrent oral and genital ulcerations, uveitis and arthritis.
- This is an autoimmune disease with circulating autoantibodies to human oral mucous membrane and immune complexes seen in 50% of the cases.

Criteria for Diagnosis

In the absence of other clinical explanations, patients must have:
1. Recurrent oral ulceration (aphthous or herpetiform) observed by the physician or patient recurring at least three times in a 12 month period.

And two of the following:
1. Recurrent genital ulceration.
2. Eye lesions: anterior uveitis, posterior uveitis, cells in the vitreous by slit lamp examination or retinal vasculitis observed by an ophthalmologist.
3. Skin lesions: erythema nodosum, papulopustular lesions (Behcet's pustulosis).
4. Pathergy, read by a physician at 24–48 hours.

Clinical Features

Mucocutaneous Lesions

- Painful oral ulcers on tongue, pharynx, buccal and labial mucosal membranes. Typical lesion is round with a sharp, erythematous and elevated border, mostly 2 to 30 mm in diameter.
- Genital ulcers occur in 60–65% of cases and are painful. In men, they are localised on the scrotum, less frequently on the penis or in the urethra, and in women on the vulva and vagina.
- Ulcers can also occur on the oesophagus, stomach and small intestine and can lead to perforation.
- Erythema nodosum.
- Behcet's pustulosis is a vasculitis characterised by a dome-shaped sterile pustule on around erythematous-oedematous base. Seen mostly on lower limbs and pubic area.

Ocular Involvement

- Often bilateral.
- Anterior uveitis, cataract, glaucoma, posterior uveitis, retinitis, venous or arterial occlusion.

Vascular Manifestations

- Vasculitis.
- Venous thrombophlebitis.
- Arterial thrombosis.

Articular Manifestations

- Non deforming arthralgia and/or arthritis occur in 45% of cases.
- Knees and ankles are most involved, although smaller joints may also be affected.
- X-ray is generally normal.

Neurologic Manifestations

- Cerebral venous thrombosis or arterial aneurysm.
- Meningitis or meningoencephalitis, seizures, hemiplegia and cranial nerve palsies.

Diagnosis

- Based on clinical features.
- Pathery test.
  - A hypersensitivity phenomenon of skin to trauma.
  - The forearm is pricked with a small and sterile needle.
  - Occurrence of a small erythematous nodule or pustule at the site of needle insertion 1–2 days after the test indicates a positive test.
    - Although a positive pathergy test is helpful in the diagnosis of Behcet's disease, only about 50% of Behcet's patients demonstrate the pathergy phenomenon.

Treatment

- For mucocutaneous manifestations, local steroids and oral colchicine are used. If not effective, levamisole, dapsone or thalidomide can be tried.
- For joint manifestations, NSAIDs are sufficient. If no response occurs, methotrexate and low-dose prednisolone may be given.
- Aspirin is given for thrombophlebitis.
- Systemic steroids along with cytotoxic drugs (methotrexate, azathioprine, chlorambucil, cyclosporin A or cyclophosphamide) for uveitis.
- Same combination for central nervous system involvement except that cyclosporin is contraindicated.

Q. What is Henoch–Schonlein purpura?

Q. Explain anaphylactoid purpura.

Features

- A small vessel vasculitis, usually seen in children.
- The characteristic features are vasculitic purpura, abdominal pain, haematuria and acute arthritis.
  - The purpuric lesions (vasculitic purpura; nonthrombocytopaenic purpura; palpable purpura) are palpable and found typically over buttocks and lower legs. These are almost always present on lateral malleolus.
  - Recurrent colicky abdominal pain is common. In some cases, this results from intussusception. This may be associated with nausea, vomiting, diarrhoea and passage of blood and mucus per rectum.
  - Arthralgia or arthritis are commonly affects the knees and ankles, but resolves without permanent damage to joints.
  - Glomerulonephritis results in haematuria and red cell casts in urine.
- With increasing age, hypertension, nephrotic syndrome and renal failure may develop rarely.
- Diagnosis can be confirmed by direct immunofluorescence of the skin biopsy sample, which demonstrates leucocytoclastic vasculitis with perivascular immunoglobulin A (IgA), C3 and fibrin deposits.

Diagnostic Criteria

Palpable purpura (essential) in the presence of one of the following:

- Diffuse abdominal pain
- Any biopsy showing predominant IgA (skin or kidney)
- Acute arthritis/arthralgia
- Renal involvement defined as proteinuria >0.3 g/24 and/or haematuria with red blood cell >5 per high power field or ≥2+ on dipstick or red blood cell casts in the urinary sediment

Treatment

- Most patients respond to bed rest and NSAIDs.
- Corticosteroids are indicated in severe systemic disease.
- Use of corticosteroids at the initial presentation does not prevent development of nephritis.

Q. What are Clutton's joints?

Q. Describe the articular manifestations of syphilis.

- Articular disease can occur in congenital, secondary and tertiary syphilis.
  - Soon after birth the infant may present with "parrot's pseudoparalysis". This is a painful limitation of joints resulting from osteochondritis.
  - At puberty typically painless bilateral effusions may occur in knees and elbows (Clutton's joints).
  - Secondary syphilis may be associated with a migrating polyarthralgia.
  - Charcot's (neuropathic) joints are painless, deformed joints seen in neurosyphilis.

Q. Discuss the clinical manifestations, diagnosis and management of systemic lupus erythematosus (SLE).

Q. List down the various autoantibodies in systemic lupus erythematosus (SLE).

- SLE is a multisystem CTD characterised by the presence of numerous autoantibodies, circulatory immune complexes and widespread immune-mediated tissue damage.
- The onset is most commonly in the second and third decades, with a female/male ratio of 9:1.

Clinical Features

Common clinical manifestations

- Systemic	Fatigue, malaise, fever, anorexia, nausea, weight loss
- Musculoskeletal	Arthralgias, myalgias, non-erosive polyarthritis, myopathy
- Mucocutaneous	Malar rash ("butterfly" rash), discoid rash, other rashes, photosensitivity, oral ulcers, alopecia
- Haematological	Anaemia, leucopenia, lymphopenia, thrombocytopenia, splenomegaly, lymphadenopathy
- Neurologic	Organic brain syndromes, psychosis, seizures, peripheral neuropathy
- Cardiopulmonary	Pleurisy, pericarditis, myocarditis, endocarditis (Libman–Sacks), pleural effusions
- Renal	Nephrotic syndrome, renal failure, proteinuria, cellular casts
- Gastrointestinal	Non-specific symptoms, bleeding or perforation, abnormal liver enzymes
- Ocular	Retinal vasculitis, conjunctivitis, episcleritis, sicca syndrome

Constitutional Symptoms

- These include fatigue, malaise, nausea, weight loss and fever.
- Though not life threatening, they have a significant impact on quality of life.

Renal Disease

- Affects about 30% of patients with SLE.
- Often asymptomatic, particularly initially; hence, regular urinalysis and blood pressure monitoring crucial.
- Characterised by proteinuria (>0.5 g/24 hours) and/or red cell casts.
- Histologically, lupus nephritis is classified as:
  - Class I—Minimal mesangial lupus nephritis.
  - Class II—Mesangial proliferative lupus nephritis.
  - Class III—Focal lupus nephritis.
  - Class IV—Diffuse lupus nephritis.
  - Class V—Membranous lupus nephritis.
  - Class VI—Advanced sclerosing lupus nephritis (≥ 90% globally sclerosed glomeruli without residual activity).

Neuropsychiatric Features

- Seen in about 20% of cases.
- Clinical features include central nervous system involvement causing headache and seizures, psychiatric features including depression and psychosis, and peripheral nervous system involvement causing neuropathy.

Musculoskeletal Features

- Arthralgia and myalgia in most patients.
- The classical "Jaccoud's arthropathy" can result in significant deformity and functional impairment. It occurs without any erosion.

Mucocutaneous Features

- Classic malar rash (fixed erythema, flat or raised, over the malar eminences, and tending to spare the nasolabial folds).
- Discoid rash (erythematous, raised patches with adherent keratotic scaling and follicular plugging).
  - Presence of only discoid rash without any systemic features occurs in discoid lupus erythematosus. The rash is primarily on the face, but can occur on any part of the body. In a small percentage of patients with discoid LE and SLE may ultimately develop.
  - Only 5% of people with DLE have SLE, but conversely among individuals with SLE, 20% will have DLE.
- Generalised photosensitivity (skin rash on exposure to sunlight).
- Alopecia.
  - Scarring, when associated with discoid lesions.
  - Diffused, often fluctuating with disease activity.
- Recurrent crops of painless mouth ulcers.
- Other oral manifestations include dryness as a result of secondary Sjogren's syndrome.

Haematological Features

- Normocytic normochromic anaemia.
- Coombs positive haemolytic anaemia.
- Thrombocytopenia.
- Leucopenia.

Cardiovascular Features

- Myocarditis and pericarditis.
- Endocarditis (Libman–Sacks endocarditis).
- A higher risk of coronary artery disease compared to general population due to increased risk of atherosclerosis and vasculitis.

Pulmonary Features

- Pleurisy.
- Pleural effusion, exudative with low C3 and positive ANA test in the fluid. Can also develop due to pulmonary embolism.

- Pneumonitis (infection must be excluded before ascribing a lung lesion to SLE).
- Vanishing lung syndrome.
- Pulmonary haemorrhage.
- Pulmonary artery hypertension.

Gastrointestinal Features

- Non-specific abdominal pain and dyspepsia.
- Hepatosplenomegaly.
- Mesenteric vasculitis.

Others

- An increased risk of haematologic cancer (particularly non-Hodgkin's lymphoma) and possibly lung and hepatobiliary cancers.

Causes of Death

- Infections and renal failure are the leading causes of death in the first decade of disease, whereas thromboembolic events are frequently the cause of death in the second and later decades.
- Atherosclerosis occurs prematurely in patients with SLE and is an independent risk factor for cardiovascular causes of death.

Investigations

Immunological Abnormalities

- The immunological abnormalities found in SLE are listed in the information box.

Autoantibodies in patients with SLE		
• Antinuclear antibodies (ANA)	• Anti-Ro (SSA)	• Antierythrocyte
• Anti-DNA (anti-dsDNA and anti-ssDNA)	• Anti-La (SSB)	• Antiplatelet
• Anti-Sm (Anti-Smith)	• Antihistone	• Antilymphocyte
• Anti-RNP	• Anticardiolipin (aCL)	• Antineuronal

- ANA is the best screening test. More than 90% of the patients have a positive test. A positive test is not specific for SLE, as it can occur in a variety of other situations like in some normal people (especially elderly), other autoimmune diseases, acute viral infections, chronic inflammatory processes and with certain drugs.
- Anti-double-stranded DNA (Anti-dsDNA) and anti-Sm are relatively specific for SLE.
- Rising levels of anti-dsDNA and low levels of complement (C3 and C4) are usually reflect disease activity.

Other Abnormalities

- The ESR is raised in some patients.
- The CRP, unlike the ESR, does not usually rise with disease activity unless there is arthritis or serositis. Infection should be excluded, if a raised CRP is found in a patient with SLE.
- Anaemia (normocytic normochromic and Coombs' positive), leucopenia, lymphopenia and thrombocytopenia may be present.
- Low C3 and C4.
- With active nephritis, urinalysis shows proteinuria, haematuria and cellular or granular casts. Blood urea and serum creatinine may be elevated. Renal biopsy confirms renal involvement.
- Prolonged partial thromboplastin time in patients with lupus anticoagulant (LA).
- Other non-specific abnormalities include false-positive tests for syphilis and positive tests for rheumatoid factor.
- Central nervous system disease usually warrants magnetic resonance imaging (MRI) of brain or spinal cord, and examination of the cerebrospinal fluid where appropriate.

Diagnostic Criteria

American College of Rheumatology Criteria

Criteria	Description
1. Malar rash	• Fixed erythema, flat or raised, over the malar eminences tending to spare the nasolabial folds
2. Discoid rash	• Erythematous raised patches with adherent keratotic scaling and follicular plugging
3. Photosensitivity	• Skin rash as a result of unusual reaction to sunlight
4. Oral ulcers	• Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Arthritis	• Nonerosive arthritis involving two or more peripheral joints
6. Serositis	• Pleuritis or pleural effusion OR • Pericarditis or pericardial effusion
7. Renal disorder	• Persistent proteinuria >0.5 g per day or >3 + if quantitation not performed OR • Cellular casts
8. Neurologic disorder	• Seizures (in the absence of offending drugs or known metabolic derangements) OR • Psychosis (in the absence of offending drugs or known metabolic derangements)
9. Haematologic disorder	• Haemolytic anaemia OR • Leucopenia (<4000/mm3) OR • Lymphopenia (<1500/mm3) OR • Thrombocytopenia (<1,00,000/mm3)
10. Immunologic disorder	• Positive LE cell preparation OR • Anti-DNA antibody OR • Anti-Sm antibody OR • False positive serologic test for syphilis
11. Antinuclear antibody	• An abnormal titre of antinuclear antibody

Presence of four or more criteria is diagnostic of SLE.

Management

- Patients with mild features (arthralgias, arthritis, myalgias, fever and mild serositis) should be managed with NSAIDs. Hydroxychloroquine may be added if required.
- Skin lesions and arthritis also respond to hydroxychloroquine.
- Photosensitive skin lesions require application of sunscreen lotions.
- Patients with severe symptoms or life-threatening features should receive corticosteroids.
- Acutely ill patients and patients with proliferative glomerulonephritis may be treated with "pulses" of methylprednisolone for 3 days (1 g/day) followed by oral steroids.

- Immunosuppressants like azathioprine, methotrexate, cyclophosphamide and mycophenolate mofetil are also useful in controlling severe disease. These agents are particularly useful in patients with renal involvement. In this regard, a combination of intravenous cyclophosphamide and steroids is the most effective regimen. Following, intravenous cyclophosphamide and oral mycophenolate mofetil is an alternative to maintain remission.
- Belimumab, a monoclonal human antibody that inactivates B-lymphocyte stimulator may be used for the treatment of patients with active disease, who are refractory to standard treatment.

Q. Explain briefly drug-induced lupus.

- Caused by several medications anti-TNF blockers, chlorpromazine, hydralazine, isoniazid, methyldopa, minocycline, procainamide and quinidine.
- Symptoms generally resolve after termination of drug.
- Significant differences between drug-induced lupus and SLE.
  - Males and females almost equally affected.
  - Renal and CNS involvement uncommon.
  - Antinuclear antibodies positive; antihistone antibodies positive; autoantibodies to DNA absent.
  - C_3 levels normal.

Q. What are antinuclear antibodies?

- Antinuclear antibodies (ANA) are antibodies that bind to various nuclear antigens. These are generally detected using indirect immunofluorescence. Most laboratories employ a HEp-2 cell line (a line of human epithelial cells).
- Higher titres of ANA (>1:160) are more likely to be true positive than low titres.
- ANA is positive in several conditions. In SLE and drug-induced lupus, its sensitivity is more than 95% while the specificity for SLE is more than 90%.
- A negative ANA test does not exclude SLE. Rarely, patients with anti-Ro (anti-SS-A) antibodies have a negative ANA.
- Titres of ANA do not correlate with disease activity and should not be used to monitor the course of SLE or other diseases.

Conditions Associated with a Positive ANA Test

- SLE	- RA
- Drug-induced lupus	- Bacterial endocarditis
- Systemic sclerosis	- Liver disease
- Sjogren's syndrome	- Interstitial lung disease
- Mixed CTD	- Malignancies
- Polymyositis/dermatomyositis	- Elderly individuals

- The nuclear pattern of a positive ANA is also important. This pattern reflects the intranuclear target of ANA. Various patterns are:
  - Homogeneous pattern—highly suggestive of SLE.
  - Rim pattern—highly suggestive of SLE. Also see with systemic sclerosis.
  - Speckled pattern—common with SLE, Sjogren's syndrome, polymyositis and mixed CTD.
  - Nucleolar pattern—common in systemic sclerosis.

Q. Describe extractable nuclear antibodies.

- Extractable nuclear antibodies are directed against small ribonuclear proteins (RNA).
- Include anti-Sm, antiuracil-rich 1 ribonucleoprotein (U1RNP), anti-SSA/Ro, anti-SSB/La, anti-tRNA synthetases (found in polymyositis/dermatomyositis), anti-topoisomerase-1 antibodies and anticentromere antibodies.
- Have a high specificity and should only be ordered in ANA positive patients with clinical features suggestive of a particular CTD and in ANA negative patients with known or suspected CTD.
- Though employed for diagnostic confirmation, they do not exclude a specific CTD.
- Do not correlate with disease activity and therefore, may be found in patients without active disease.

Q. Discuss briefly about various antibodies seen in patients with connective tissue diseases.

Autoantibodies in Various Connective Tissue Diseases (CTD)

Autoantibodies	Importance
• Rheumatoid factor	• Discussed separately
• Anticyclic citrullinated peptide	• Discussed separately
• Antinuclear antibodies	• Discussed above
• Anti-double-stranded DNA (anti-dsDNA)	• Highly specific for SLE • Positive in only about 60% cases of SLE • Low titres also seen in Sjogren's syndrome, RA • Levels often correlate with disease activity • Presence correlates with lupus nephritis • Usually absent in drug-induced SLE
• Antihistone	• Sensitive for drug-induced lupus, but not specific • Useful in patients with a positive ANA and a history of exposure to medications that can produce lupus
• Anti-Smith (anti-Sm)	• Specific for SLE but present in only 20–30% cases
• Anti-U1 ribonucleoproteins (RNP)	• Present in 20–30% case of SLE • High titres in syndromes with features of polymyositis, lupus, scleroderma and mixed CTD • In anti-DNA-negative SLE, indicates low risk of nephritis.
• Anti-Ro (anti-SS-A)	• Common in Sjogren's syndrome with extraglandular features • Positive in 40% cases of SLE and is associated with photosensitive rash and pulmonary disease • May be positive in ANA-negative lupus • Indicates higher risk of lupus nephritis • May be positive in neonatal lupus or congenital heart block due to maternal antibodies
• Anti-La (anti-SS-B)	• Present in 10–15% cases of SLE • Presence indicates low risk of nephritis • Associated with Sjogren's syndrome
• Antiphospholipid	• Present in nearly 50% cases of SLE • Three types: lupus anticoagulant (LA), anticardiolipin (aCL) and false-positive for syphilis • LA and IgG aCL associated with APLA syndrome
• Anticentromere	• Found in 20–35% cases of systemic sclerosis • Associated with CREST syndrome (calcinosis, Raynaud's phenomenon, oesophageal dysfunction, sclerodactyly and telangiectasia) • Also present in primary biliary cirrhosis
• Anti-topoisomerase I (anti-scl-70)	• Highly specific for systemic sclerosis • Found in 20–40% cases of systemic sclerosis • Associated with diffuse cutaneous, pulmonary and cardiac involvements

Autoantibodies	Importance
• Anti-Jo1	• Present in 30% case with polymyositis or dermatomyositis. • Associated with Raynaud's phenomenon
• Antineutrophil cytoplasmic antibodies (ANCA)	• Discussed separately

Q. Describe antiphospholipid antibody (APLA) syndrome and antiphospholipid antibodies.

- Antiphospholipid antibody (APLA) syndrome or antiphospholipid syndrome (APS) is characterised by presence of antiphospholipid antibodies and a syndrome of hypercoagulability.
- Primary antiphospholipid syndrome occurs in patients without clinical evidence of another autoimmune disease.
- Secondary antiphospholipid syndrome occurs in association with other autoimmune diseases like SLE.

Clinical Features

Organ/system	Manifestations
• Arterial/venous	Thrombosis in any artery or vein
• Cardiac	Angina, myocardial infarction, valvular vegetations
• Haematologic	Thrombocytopenia (in 40–50%) haemolytic anaemia, disseminated intravascular coagulation
• Neurologic	Transient ischaemic attack, stroke, headache, mononeuritis multiplex
• Obstetrical	Pregnancy loss, intrauterine growth retardation
• Ophthalmologic	Retinal artery/vein thrombosis
• Renal	Thrombosis of renal artery/vein, renal infarction, acute renal failure, haematuria
• Gastrointestinal	Budd–Chiari syndrome, hepatic infarction, intestinal infarction, splenic infarction, pancreatitis
• Cutaneous	Ulcers and infarcts in the skin, gangrene
• Pulmonary	Pulmonary embolism, pulmonary hypertension

Diagnosis

Antiphospholipid Antibodies

- These are a heterogeneous group of autoantibodies directed against phospholipids-binding proteins.
- These are LA, aCL antibodies and anti-β_2-glycoprotein I antibodies.
- LA antibodies.
    - Identified by coagulation assays in which they prolong the clotting times.
    - Failure of the prolonged clotting time to correct after a 1:1 mix with normal platelet-free plasma and correction of the clotting time after addition of excess phospholipids confirms the presence of LA.
    - For LA screening, two or more phospholipid-dependent coagulation tests, including the activated partial thromboplastin time, dilute Russell viper venom time and kaolin clotting time required.
- aCL antibodies target cardiolipin (a bovine cardiac protein) are detected by immunoassays.
- Anti-β_2-glycoprotein I antibodies are directed against β_2-glycoprotein I and may be causal in APLA syndrome.
- LA antibodies are more specific while aCL antibodies are more sensitive for antiphospholipid syndrome. IgG aCL antibodies are more specific compared to IgM type.
- Antiphospholipid antibodies may be found in 10% of normal population and 30–50% patients with SLE.
- These antibodies are also found in patients with infections such as human immunodeficiency virus and may develop during therapy with medications such as chlorpromazine.

Criteria for Diagnosis

Clinical features	Laboratory features

• Vascular thrombosis (arterial, venous or small vessel)
• Complications of pregnancy.
  • One of more unexplained deaths of morphologically normal foetuses at birth or after 10 weeks of gestation
OR
  • One or more premature births of morphologically normal neonates at or before 34th weeks of gestation
OR
  • Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation
	• aCL antibodies (on two or more occasions at least 12 weeks apart)
	• LA antibodies (on two or more occasions at least 12 weeks apart)
	• Anti-β_2-glycoprotein I (IgG and/or IgM) on two or more occasions at least 12 weeks apart

- A diagnosis of definite antiphospholipid syndrome is made if the patient has one clinical and one laboratory criteria.

Treatment

Treatment of Venous Thrombosis
- Anticoagulation with heparin and oral warfarin, followed by oral warfarin to maintain International normalised ratio (INR) between 2 and 3. Duration of treatment is probably lifelong.
- Steroids are often added to this treatment.
- In severe cases of generalised thrombosis, plasmapheresis or intravenous immunoglobulin may be tried.

Prevention of Recurrence of Arterial Thrombosis
- Aspirin 325 mg/day plus warfarin with INR between 1.4 and 2.8.

Prophylaxis of Any Thrombotic Episode
- Aspirin may be useful in preventing thrombosis in females with previous pregnancy loss.
- In presence of underlying SLE with antiphospholipid antibodies positive, aspirin along with hydroxychloroquine should be started.
- Modification of other risk factors like hypercholesterolemia, smoking, etc.

Management of Pregnancy in Patients with Antiphospholipid Syndrome
- Females with antiphospholipid antibodies and a history of two or more early pregnancy losses, or one or more late pregnancy losses that have no prior history of thrombosis should receive combination of aspirin and heparin (unfractionated or low molecular weight) during pregnancy.
- Aspirin should be started with attempted conception.
- Heparin (5,000–10,000 units every 12 hours) or low-molecular-weight heparin in prophylactic doses (enoxaparin 1 mg/kg; dalteparin 5000 units once a day) should be started, when a viable intrauterine pregnancy is documented on ultrasound and continued until late in the third trimester.

Catastrophic Antiphospholipid Syndrome
- Can occur at onset or some time after diagnosis.
- Presents with rapidly progressive multiorgan involvement with histopathologic evidence of small vessel occlusions.
- Common clinical features include intra-abdominal features (involvement of kidney, liver, gastrointestinal tract and spleen), ARDS, cerebral manifestations (multiple microinfarctions, seizures), cardiac involvement (cardiac failure, infarction) and skin complications (livedo reticularis, skin necrosis).

- Thrombocytopenia, haemolysis, schistocytes and activation of coagulation system are common laboratory findings.
- High ferritin is common.
- Despite treatment, mortality is nearly 50%.
- The mainstay of treatment is intravenous heparin along with high-dose corticosteroids. Early addition of plasma exchange and/or intravenous immunoglobulin should be considered in patients who do not respond promptly to heparin and corticosteroids.

Q. Write a short note on scleroderma.

Q. Describe CREST syndrome.

Q. Discuss the clinical manifestations, diagnosis and management of systemic sclerosis.

- Systemic sclerosis is a multisystem disorder affecting skin (scleroderma), gastrointestinal tract, musculoskeletal system, lungs, heart and kidneys. The disease can also occur in a localised form without systemic involvement (localised scleroderma).
- Two subsets of the systemic form of the disease have been identified. They are diffuse cutaneous systemic sclerosis and limited cutaneous systemic sclerosis.
- Two subsets of the localised scleroderma are morphoea and linear scleroderma.

Clinical Manifestations

- Raynaud's phenomenon is usually the first manifestation. It may precede other features by months or years.
- Diffuse cutaneous scleroderma is characterised by rapid development of symmetrical skin thickening of proximal and distal extremities, face and trunk. These patients also have a high risk of developing kidney, interstitial lung disease and other systemic involvement.
- Limited cutaneous scleroderma is associated with skin thickening limited to distal extremities and face. A few patients may develop interstitial lung disease, pulmonary arterial hypertension (due to fibrosis of pulmonary artery) or biliary cirrhosis after several years. This subset may also have features of CREST syndrome (i.e. calcinosis, Raynaud's phenomenon, (o)esophageal dysfunction, sclerodactyly and telangiectasia).

Skin Manifestations

- In the early stages (oedematous phase), there is non-pitting oedema and induration of the skin.
- As the disease advances (indurative phase), the skin becomes firm, thickened and eventually tightly bound to underlying subcutaneous tissue.
- After many years of disease, the skin may become thin and atrophic.
- Facial skin changes result in taut skin, "mask-like" face, "beaking" of the nose and microstomia.
- Other skin manifestations are flexion contractures, ulcers over fingertips and bony prominences, pigmentation, telangiectasia, calcinosis cutis and dry coarse skin.

Musculoskeletal Manifestations

- Muscle weakness occurs due to disuse atrophy, myopathy and myositis.
- Arthralgia of fingers and knees, symmetric polyarthritis, "leathery" crepitations over joints (especially knees) and resorption of terminal phalanges.

Gastrointestinal Manifestations

- Oesophageal involvement can manifest as dysphagia, reflux oesophagitis, sliding hiatus hernia, peptic oesophagitis, strictures, dilatation and atony of lower oesophagus.
- Gastric involvement results in dilatation, atony and delayed gastric emptying.
- Small and large bowel involvements result in abdominal distension, abdominal pain, constipation, intestinal obstruction, malabsorption and steatorrhoea.

Pulmonary Involvement

- Pulmonary fibrosis manifests as exertional breathlessness, bilateral basal crepitations and "honeycomb" lung on chest radiograph.

- Other pulmonary manifestations are aspiration pneumonia, pulmonary hypertension with right-heart failure, and alveolar cell and bronchial carcinoma.

Other Manifestations

- Cardiac involvement can manifest as pericarditis with or without effusion, heart failure, heart blocks, arrhythmias and cardiomyopathy.
- Renal involvement can manifest as progressive renal failure, or renal crisis manifesting as acute renal failure with malignant hypertension, hypertensive encephalopathy and left ventricular failure.
- Rare manifestations are dryness of mouth and eyes, hypothyroidism, cranial and peripheral nerve involvement, and impotence in males.

Investigations

- Elevated ESR.
- Anaemia related to:
  - Chronic disease.
  - Iron deficiency due to gastrointestinal bleed.
  - Blind loop syndrome producing folate and B_{12} deficiency.
  - Microangiopathic haemolytic anaemia due to renal involvement.
- Antinuclear antibodies in 90% cases and rheumatoid factor in 25% cases.
- Antinuclear antibodies which are highly specific for systemic sclerosis include anti-topoisomerase I (previously called anti-Scl-70) and anticentromere.
  - Anti-topoisomerase I antibodies (anti-topo I) are found in about 40% of patients with diffuse cutaneous systemic sclerosis and less than 10% of patients with limited cutaneous systemic sclerosis.
  - Anticentromere antibodies are seen in 30–40% of patients with limited cutaneous involvement.
  - Anticentromere and anti-topo I antibodies are always mutually exclusive, being present in less than 0.5% of all patients with systemic sclerosis simultaneously.
- Anti-U1 RNP is found in very small percent of cases but is present in virtually all patients with mixed CTD.
- Nailfold capillaroscopy shows characteristic of nailfold capillary abnormalities including capillary dilatation and loop dropout.
- Barium swallow test is used to demonstrate various abnormalities in oesophagus.
- X-ray and computed tomogram of chest for interstitial lung disease.
- Pulmonary function tests including diffusion capacity for interstitial lung disease.
- Echocardiography for cardiac involvement and pulmonary hypertension.

Treatment

- Monitoring of blood pressure, blood counts, renal functions and analysis of urine on regular basis.
- Control of Raynaud's phenomenon.
- Management of gastroesophageal reflux.
- D-penicillamine may be used to reduce skin thickening. It may also reduce systemic involvement.
- Cyclophosphamide remains the treatment of choice for lung disease and severe skin disease.
- Methotrexate is the treatment of choice for scleroderma overlap syndromes, whereas mycophenolate and azathioprine are also used for both skin and lung disease, alone or for maintenance therapy after cyclophosphamide induction.
- Steroids are indicated in patients with myositis, pericarditis or pulmonary fibrosis. However, they should not be used for skin involvement.
- Antihypertensives in renal crisis (most important drugs are ACE inhibitors).

Q. What are inflammatory muscle diseases?

- A heterogenous group of muscle diseases characterised by inflammation.
- Three major forms are: polymyositis, dermatomyositis and inclusion body myositis.

Common Inflammatory Muscle Diseases

Infective forms	Autoimmune (idiopathic)
- Viral (Coxsackie B, influenza A & B, HIV) - Bacterial (*Streptococcus, Staphylococcus,* Clostridia, Mycobacterial) - Fungal (Candidiasis, coccidioidomycosis) - Protozoal (Toxoplasmosis) - Helminthic (Trichinosis, cysticercosis)	A. Generalised - Dermatomyositis - Polymyositis - Inclusion body myositis - Overlap syndromes - Necrotising myopathy (paraneoplastic, drugs, toxins) - Eosinophilic myositis - Granulomatous myositis B. Focal forms - Monomelic myositis - Eosinophilic myositis - Macrophagic myofasciitis - Orbital myositis

Q. How do you classify polymyositis and dermatomyositis? Discuss the clinical manifestations, diagnosis and management of polymyositis–dermatomyositis.

- Polymyositis and dermatomyositis are conditions in which the skeletal muscle is damaged by an inflammatory process dominated by lymphocytic infiltration.
- The term polymyositis is applied when the condition spares the skin, and the term dermatomyositis, when polymyositis is associated with a characteristic skin rash.

Classification of Idiopathic Inflammatory Myositis

• Group I	Primary idiopathic polymyositis
• Group II	Primary idiopathic dermatomyositis
• Group III	Dermatomyositis (or polymyositis) associated with neoplasia
• Group IV	Juvenile dermatomyositis (or polymyositis) associated with vasculitis
• Group V	Polymyositis (or dermatomyositis) with associated collagen vascular disease
• Group VI	Inclusion body myositis
• Group VII	Miscellaneous

Clinical Manifestations

Primary Idiopathic Polymyositis

- Weakness of the proximal muscles of the lower limbs (hips and thighs) results in difficulty in arising from the squatting or kneeling position and in climbing or descending stairs.
- Weakness of the proximal muscles of the upper limbs (shoulder girdle muscles) results in difficulty in placing an object on a high shelf or combing hair.
- Weakness of the trunk muscles and flexor muscles of the neck may be present.
- Pain and tenderness of the involved muscles of buttocks, thighs and calves may be present.
- The distal muscles are spared in most of the patients.
- Involvement of facial and ocular muscles is uncommon.
- Other features are dysphagia (due to weakness of oropharyngeal muscles and striated muscle of upper third of oesophagus), respiratory impairment, myocarditis resulting in ECG abnormalities, heart failure, arrhythmias, arthralgia and interstitial lung disease.
- Muscle biopsy shows single fibre muscle necrosis and infiltration with CD8 + lymphocytes.

Primary Idiopathic Dermatomyositis

- This term is used when polymyositis is associated with characteristic skin changes.
- The skin changes may precede or follow the muscle syndrome and include a localised or diffuse erythema, maculopapular eruption or scaling eczematoid dermatitis.

- The classic lilac-coloured (heliotrope) rash is seen on the upper eyelids. Periorbital oedema is frequent.
- Other pathognomonic cutaneous manifestations include:
  - Gottron's papules are violaceous papules overlying the dorsal interphalangeal or metacarpophalangeal areas. When fully formed, these papules become slightly depressed at the center, which can assume a white, atrophic appearance. Associated telangiectasia can be present.
  - Gottron's sign is symmetrical, erythematous or violaceous, often atrophic, macules or plaques overlying dorsal aspect of interphalangeal and metacarpophalangeal joints, olecranon processes, patellae, and medial malleoli.
  - Periungual telangiectasias.
  - Shawl sign is the occurrence of erythematous macules distributed in a "shawl" pattern over the shoulders and back. The V sign is occurrence of erythematous lesions over the upper chest and neck.
  - The hands may be fissured, scaly and hyperkeratotic (mechanic's hand).
- Calcium deposition (calcinosis cutis) may occur on the buttocks, elbows, knees or traumatised areas and is more common in children.
- Muscle biopsy shows muscle necrosis (single fibres or in groups), perifasicular atrophy, and infiltration with B cells and CD4 + lymphocytes
- Pathognomonic skin lesion without muscle involvement is known as amyopathic dermatomyositis or dermatomyositis sine myositis.
- A few patients over the age of 50 years with dermatomyositis have an underlying malignancy. The most commonly reported malignancies are ovarian and gastric carcinoma, small cell lung cancer and lymphoma. Malignancies can also rarely develop in patients with polymyositis.

Diagnosis

- ESR is usually raised.
- Antinuclear antibodies are frequently raised.
- Elevated serum levels of the muscle enzymes such as creatine kinase (CK), aldolase, serum glutamic oxaloacetic transaminase (SGOT), lactic dehydrogenase (LDH) and serum glutamic pyruvate transaminase (SGPT).
- Autoantibodies directed against cytoplasmic RNA synthetases, other cytoplasmic proteins and RNP seen in about 30% of patients. Only anti-histidyl-tRNA synthetase (anti-Jo-1 antibody) is a diagnostic marker that is present in 20% of patients with polymyositis/dermatomyositis, and is associated with interstitial lung disease, arthritis, mechanic's hands and Raynaud's phenomenon.
- Characteristic EMG findings (myopathic pattern) may be present.
- Muscle biopsy shows the typical pathologic changes of myositis.

Management

- The treatment of choice is prednisolone at a dose of 1 mg/kg daily till patient shows significant improvement. Then the dose is tapered to 10–15 mg/day.
- If no improvement occurs with prednisolone, azathioprine (2–3 mg/kg/day) may be added. It also has some steroid-sparing effect.
- Other useful drugs include methotrexate, mycophenolate mofetil, cyclosporin and tacrolimus. Because 50% of anti-Jo-1 positive patients either have or will develop interstitial lung disease, methotrexate should be avoided in such patients.
- In severe cases, intravenous immunoglobulins.

Q. Write a brief note on polymyalgia rheumatica.

- This is a descriptive term for an aching syndrome usually seen in the elderly patients, with an elevated ESR that cannot be attributed to more defined rheumatic, infectious or neoplastic disorders.
- Women are two to three times more likely than men to be affected by it.

Clinical Features

- Proximal myalgias are characteristic. There is chronic, symmetric, proximal muscle aching and stiffness, usually involving shoulder, pelvic girdles and neck. Muscles may be tender on palpation.
- Constitutional symptoms like malaise, fatigue, anorexia, weight loss, fever and night sweats may be present.
- Neuropsychiatric manifestations are frequent, particularly depression.
- A considerable number (15–30%) may have peripheral arthritis mainly involving knee, wrist, pitting oedema and carpal tunnel syndrome.
- 10–30% of these patients have associated temporal arteritis.

Investigations

- Elevated ESR (more than 50 mm/hour), CRP, and normocytic-normochromic anaemia.
- Tests for rheumatoid factor and antinuclear antibodies may be positive.
- Temporal artery biopsy may show evidence of giant cell arteritis.
- Muscle enzymes are characteristically normal.

Treatment

- Prednisolone is given at dose of 10–15 mg/day is rapidly effective. A prompt and dramatic clinical response is considered by some to be an absolute criterion for diagnosis. Symptoms resolve in 48–72 hours and the ESR normalises after 7–10 days. Duration of therapy is 2–3 years.
- NSAIDs are useful to suppress rheumatic symptoms.

Q. Explain temporal arteritis, cranial arteritis or giant cell arteritis.

- This is a disease of the elderly, occurring almost exclusively in people over the age of 55 years. It is closely associated with polymyalgia rheumatica.
- Arteritis can occur in any large and medium artery although it has a predilection for the extracranial carotid artery and its branches such as the superficial temporal, occipital, ophthalmic, posterior ciliary arteries, and vertebral arteries.
- The disease is characterised by the classic complex of fever, anaemia, high ESR and headache (usually temporal) in an elderly patient.
- The temporal artery may become tender, thickened and cordlike or nodular.
- Scalp pain, claudication of tongue and jaw are frequent.
- Visual symptoms including diplopia and even sudden blindness may result from ischaemic optic neuritis. The contralateral eye is often affected within one to two weeks making prompt recognition and treatment critical.
- Involvement can extend to the aorta, its primary and secondary branches including subclavian and axillary arteries, which leads to upper extremity ischaemia, absent or asymmetrical pulses and blood pressure readings.
- Neurological manifestations occur in about 30% of patients and include mononeuropathies, peripheral polyneuropathies of upper or lower extremities, and occasionally, transient ischaemic attacks and strokes.
- Thoracic aortic aneurysm or dissection is typically a late complication.
- The diagnosis is confirmed by biopsy of the temporal artery.
- Duplex ultrasonography can detect the characteristic appearance of a hypoechoic "halo", occlusions and stenosis of temporal artery.
- This condition is exquisitely sensitive to corticosteroid therapy. Prednisolone is given at a dose of 40–60 mg/day. Dramatic response to a trial of prednisolone can confirm the diagnosis other than a temporal artery biopsy.

Q. Discuss the clinical features, diagnosis and management of classic polyarteritis nodosa (PAN).

- Polyarteritis nodosa (PAN) is a multisystem, necrotising vasculitis of small and medium-sized muscular arteries. The organ systems commonly involved are kidneys, heart, liver and gastrointestinal tract. It does not involve pulmonary arteries.
- Most cases of PAN are idiopathic, although hepatitis B or C virus infection and hairy cell leukaemia are important in the pathogenesis of some cases.

Clinical Features

- Polyarteritis nodosa (PAN) predominantly affects males (M:F = 2.5:1).
- Common clinical manifestations are skin involvement, hypertension, renal failure, polyarthritis, myalgia, peripheral neuropathy and mononeuritis multiplex.
  - Skin manifestations include tender erythematous nodules, palpable purpura and ulcers.
  - Renal involvement leads to renal ischaemia, infarcts, hypertension and renal insufficiency
- Less commonly, clinical features result from involvement of gastrointestinal system, skin, heart, genitourinary system and central nervous system.

Diagnosis

- Anaemia, raised ESR and neutrophil leucocytosis.
- 30% of these patients are positive for hepatitis B surface antigen (HBsAg).
- p-ANCA is present in only about 20% of cases.

- Arteriograms usually reveal aneurysms in the kidneys and abdominal viscera.
- Characteristic finding of vasculitis on biopsy material of involved organ confirms the diagnosis.

Treatment

- Various treatment modalities include corticosteroids, cyclophosphamide and plasma exchange (see microscopic poly-angiitis).

Q. Describe microscopic polyangiitis.

- It is the most common ANCA-associated, necrotising, small vessel vasculitis and is characterised by absence of immune deposits in the involved vessels.

Clinical Features

- The most common age of onset is 40–60 years. It is more common in males compared to females.
- Presentation is by variable combinations of renal involvement, malaise, low-grade fever, weight loss, palpable purpura, abdominal pain, cough and haemoptysis.
- Kidney involvement is present in nearly 90% cases. It manifests in the form of microscopic haematuria with cellular casts in combination with proteinuria and rapidly progressive glomerulonephritis.
- Pulmonary haemorrhage (diffuse alveolar haemorrhage) is a very serious condition particularly in those patients who also have rapidly progressive glomerulonephritis (pulmonary-renal syndrome).
- Others: mononeuritis multiplex.

Diagnosis

- Most patients have positive p-ANCA although c-ANCA may also be present in 40% cases.

Treatment

- Combined treatment with cyclophosphamide and corticosteroids has reduced mortality and morbidity significantly.
- In severe cases, high dose (500–1000 mg) intravenous methylprednisolone for 3 days combined with intravenous cyclo-phosphamide (500–1000 mg/m^2 body surface area) is recommended to induce remission. The regimen is repeated once every 4 weeks though pulses of steroids can be repeated after 1 week.
- In severe cases (e.g. renal failure or diffuse alveolar haemorrhage), additional use of plasma exchange is beneficial. It may not be of value in patients with Churg–Strauss syndrome and PAN.
- Maintenance is with tapering doses of steroids along with oral cyclophosphamide for 12–18 months.
- Other treatment regimens that may be useful in some patients include methotrexate, azathioprine, rituximab and intra-venous immunoglobulin.

Q. Discuss Churg–Strauss syndrome.

- Churg–Strauss syndrome (CSS) or allergic granulomatous angiitis or eosinophilic granulomatosis with polyangiitis is a rare syndrome that affects small and medium-sized arteries and veins.
- It is a systemic disorder characterised by asthma, transient pulmonary infiltrates, hypereosinophilia and a systemic vasculitis.

Clinical Features

- The patient has a history of asthma and allergic rhinitis that is followed by small vessel vasculitis and granulomatous inflammation.
- Unlike in classical bronchial asthma, in CSS, it does not show the typical seasonal exacerbations
- The vasculitic phase usually develops within 3 years of onset of asthma.
- Vasculitis, granuloma and eosinophilia may involve any organ system including lung, CNS, kidney, lymph nodes, muscle and skin. Common features are:
  - Arthralgia, arthritis.
  - Purpura.
  - Peripheral, patchy, and migratory infiltrates in the lungs
  - Myocarditis, congestive heart failure, pericarditis and myocardial infarction.
  - Abdominal pain, diarrhoea and GI bleed.
  - Mononeuritis multiplex.

- Deep vein thrombosis and pulmonary embolism.
- Isolated urinary abnormalities (i.e. microscopic haematuria, proteinuria) and rapidly progressive glomerulonephritis.
- Stroke.
- Coronary arteritis and myocarditis are the principal causes of morbidity and mortality.

Investigations

- Eosinophils >10% in peripheral blood.
- Elevated ESR and CRP.
- Urine showing RBC casts and proteinuria.
- Increased IgE levels.
- Positive antinuclear cytoplasmic antibodies against myeloperoxidase (p-ANCA) in 15–60% of cases.
- Chest X-ray may show infiltrates and pleural effusion.

Diagnostic Criteria*

• Asthma	• Nonfixed pulmonary infiltrates
• Eosinophilia greater than 10% on a differential WBC count	• Paranasal sinus abnormalities
• Mononeuropathy or polyneuropathy	• Biopsy containing a blood vessel with extravascular granulomas

*The finding of four of the six criteria has a sensitivity of 85% and a specificity of >99%.

Treatment

- Most patients respond to high-dose steroids, though some cases may require addition of cytotoxic drugs like cyclophosphamide.
- In severe cases, anti-TNF-α agents like infliximab and etanercept.

Q. Write briefly on clinical features, diagnosis and treatment of Wegener's granulomatosis or granulomatosis with polyangiitis.

- This entity is characterised by granulomatous vasculitis of upper and lower respiratory tracts together with glomerulonephritis.

Clinical Features

- Constitutional symptoms including fever, migratory arthralgias, malaise, anorexia and weight loss
- Paranasal sinus pain and discharge, nasal mucosal ulcerations, saddle nose deformity and hearing loss.
- Pulmonary involvement may produce hoarseness, cough, haemoptysis, wheezing and dyspnoea.
- Renal involvement occurs in the form of glomerulonephritis resulting in proteinuria, haematuria and red blood cell casts in the urine. Rapidly progressive glomerulonephritis and acute renal failure may occur.
- Other manifestations are palpable purpurae, conjunctivitis, episcleritis, scleritis, cranial neuritis and mononeuritis multiplex.

Diagnosis

- The ESR is markedly elevated.
- Other non-specific abnormalities include mild anaemia, leucocytosis and mild hypergammaglobulinaemia.
- Chest radiograph may reveal patchy or diffuse pulmonary opacities, fleeting pulmonary infiltrates and nodules that may cavitate.
- A CT scan of chest may reveal many cavitating nodules not visible on plain chest X-ray.
- A CT scan of the sinuses may reveal mucosal thickening, bone destruction and infiltration of the orbits.
- Serum antiproteinase 3 (c-ANCA) is positive in nearly 95% cases.
- The diagnosis can be confirmed by lung biopsy, which will show the characteristic necrotising granulomatous vasculitis. Renal biopsy shows a segmental necrotizing crescentic glomerulonephritis, with no immunoglobulin deposition ("pauci-immune").

Treatment

- Treatment is similar to that for microscopic polyangiitis.

Q. Define and classify vasculitis.

- Vasculitis is a clinicopathologic process characterised by inflammation of blood vessel wall and the surrounding interstitium.
- May affects large, medium or small-sized arteries, arterioles, venules or veins.
  - The large vessels include the aorta and its largest branches (clinically affecting the extremities and head/neck).
  - The medium-sized vessels refer to the main visceral arteries (e.g. renal, hepatic, coronary, mesenteric).
  - The small vessels refer to the capillaries, venules and arterioles.
- Small-vessel vasculitis may be associated with autoantibodies.

Classification

Large vessel vasculitis	Small vessel vasculitis	
• Takayasu's disease • Temporal arteritis **Medium vessel vasculitis** • Polyarteritis nodosa (PAN) • Kawasaki's disease • Primary CNS vasculitis	*ANCA-associated* • Wegener's granulomatosis • Microscopic polyangiitis • Churg–Strauss syndrome (CSS) • Drug-induced vasculitis (cefotaxime, minocycline, carbimazole, methimazole, propylthiouracil, adalimumab, etanercept, infliximab, clozapine, thioridazine, allopurinol, D-penicillamine, hydralazine, levamisole, phenytoin and sulphasalazine)	*Non-ANCA-associated:* *Immune complex deposition (hypersensitivity vasculitis)* • Henoch–Schonlein purpura • SLE • RA • Mixed cryoglobulinaemia • Goodpasture syndrome • Behcet's disease *Others* • Drug-induced vasculitis • Infection-induced vasculitis • Inflammatory bowel disease

ANCA— Antineutrophil cytoplasmic antibodies

Q. Discuss briefly the clinical features associated with small vessel vasculitis. What are the laboratory investigations in a case with vasculitis? How do you treat it?

- Small vessel vasculitis is defined as vasculitis that affects vessels smaller than arteries (i.e. arterioles, venules and capillaries).

Clinical Features

• Constitutional features	Fever, anorexia, malaise, weight loss
• Musculoskeletal features	Myalgias, arthralgias, arthritis
• Skin	Palpable purpura, urticaria
• Kidneys	Haematuria, proteinuria, renal failure, necrotising glomerulonephritis (in ANCA-positive cases)
• Nervous system	Peripheral neuropathy, cranial nerve involvement, mononeuritis multiplex Hypertension
• Cardiovascular system	Cough, haemoptysis, dyspnoea, lung infiltrates, diffused alveolar
• Respiratory system	haemorrhage

Laboratory Investigations

- Haemoglobin, total and differential leucocyte count, platelet count, and ESR.
- Routine chemistry profile.
- Urinalysis.
- Chest radiograph and paranasal sinuses radiograph.
- Antinuclear antibodies, rheumatoid factor, ANCA and cryoglobulins.
- Antibody to hepatitis B and C.
- ELISA for human immunodeficiency virus.
- Other tests depend on clinical circumstances and include nerve conduction velocity, nerve biopsy, angiography, skin biopsy and kidney biopsy.

Management

- It depends on the underlying cause of vasculitis.
- Most commonly used drugs include corticosteroids, azathioprine, cyclophosphamide, and other immunosuppressants.

Q. What are antineutrophil cytoplasmic antibodies (ANCA)? Discuss their significance.

- ANCA are specific antibodies against antigens in cytoplasmic granules of neutrophils and lysosomes of monocytes.
- Two major patterns of staining are seen:
  - Cytoplasmic ANCA (c-ANCA) are mainly antibodies to proteinase 3.
  - Perinuclear ANCA (p-ANCA) are antibodies to myeloperoxidase.
- For their significance in small vessel vasculitis, ANCA should be assayed both with indirect immunofluorescence (screening test) and then direct ELISA for proteinase-3 or myeloperoxidase.
- Significance.
  - A number of conditions are associated with ANCA positivity (see above).
  - ANCA is present in majority of patients with microscopic polyangiitis, Wegener's granulomatosis and Churg–Strauss syndrome. However, a negative ANCA does not exclude these diagnoses. Similarly, a positive ANCA assay is not solely diagnostic of ANCA-associated diseases.
  - ANCA detected by indirect immunofluorescence may be seen in RA, Felty's syndrome, SLE, ulcerative colitis, chronic hepatitis, primary sclerosing cholangitis, HIV infection, active tuberculosis and subacute bacterial endocarditis.

Q. Discuss the aetiology, clinical manifestations, diagnosis and management of gout.

Q. Give a brief account of the various causes, clinical manifestations, investigations and management of hyperuricaemia.

Aetiology of Gout and Hyperuricaemia

Increased production of uric acid	Decreased renal excretion of uric acid

• **Increased purine synthesis de novo**
   • Hypoxanthine-guanine phosphoribosyl transferase (HGPRT) deficiency
   • Phosphoribosyl pyrophosphate (PRPP) synthetase overactivity
   • Glucose-6-phosphatase deficiency
   • Idiopathic
 • **Increased turnover of purines**
   • Myeloproliferative disorders
   • Lymphoproliferative disorders
   • Cancer chemotherapy
   • Haemolysis
	• Renal failure
	 • Lead poisoning
	 • Alcohol
	 • Drugs—diuretics, low-dose aspirin, pyrazinamide, cyclosporin, levodopa
	 • Lactic acidosis
	 • Hyperparathyroidism
	 • Myxoedema
	 • Down's syndrome
	 • Unidentified inherited defects

Clinical Features

- The full natural history of gout comprises four stages:
  1. Asymptomatic hyperuricaemia.
  2. Acute gouty arthritis.
  3. Intercritical period.
  4. Chronic tophaceous gout (tophi and chronic gouty arthritis).
- The onset may be insidious or explosively sudden.
- The metatarsophalangeal joint of the great toe is the site of the first attack of acute gouty arthritis (podagra) in 70% of patients.
- Other joints that can get affected include tarsal joints, ankles, knees and wrists. Central joints such as hips, shoulders and spine are seldom affected, possibly because higher temperatures in these joints are not conducive to crystallisation.

- The affected joint is hot, red and swollen with shiny overlying skin and dilated veins. The joint is excruciatingly painful and tender. These joint manifestations may be associated with anorexia, nausea, fever, leucocytosis and raised ESR.
- The joint manifestations may last only a day or two, or up to several weeks, but characteristically subside spontaneously.
- Gout can also cause bursitis and tenosynovitis.
- This is followed by an asymptomatic phase (intercritical period) that is diagnostically important.
- In chronic tophaceous gouty arthritis, crystal deposits appear in cartilage, synovial membranes, tendons and soft tissues. The classic location of a tophus is the helix and antihelix of the ear.

Nephropathy

- Nephropathy is seen in 90% of subjects with gouty arthritis. Two types of parenchymal renal damage have been described:
  - Urate nephropathy results from deposition of urate crystals in the interstitial tissue, leading to albuminuria, isosthenuria or renal failure.
  - Obstructive uropathy (nephrolithiasis) results from the formation of uric acid crystals in the collecting tubules, renal pelvis or ureter with blockage of urine flow. The formation of urate calculi is favoured by hyperuricosuria, purine overproduction, excessive purine ingestion, uricosuric drugs and acidic urine.

Other Features

- Gout may be associated with increased incidence of hypertension and cardiovascular disorders.
- On the other hand, hypertension is also a risk factor for development of gout.

Diagnosis

Cardinal features of gout
• Increase in serum uric acid concentration (>7.0 mg/dL in males and >6.0 mg/dL in females) • Recurrent attacks of a characteristic acute arthritis, in which crystals of monosodium urate monohydrate are demonstrable in leucocytes of synovial fluid • Aggregated deposits of monosodium urate monohydrate (tophi) in and around the joints • Renal disease involving interstitial tissue and blood vessels • Uric acid nephrolithiasis

- Serum uric acid levels are elevated. However, during an acute attack serum uric acid may be normal in 50% cases.
- Synovial fluid examination done by compensated polarised microscopy can demonstrate urate crystals. They are seen as slender, needle-shaped and negatively birefringent structures.
- Plain radiographs are helpful to differentiate chronic tophaceous gout from RA.
  - Erosions in gout are characteristically punched out with overhanging sclerotic margins and are situated away from joint margins, sometimes outside the joint capsule.
  - RA causes marginal erosions, always within the limits of the joint capsule. Periarticular osteopenia is absent and joint space is preserved in gout.

Management

Treatment of Acute Attack

- NSAIDs are the agents of choice. All NSAIDs are equally effective. Commonly used NSAIDs are indomethacin (50 mg 6 hourly), naproxen and fenoprofen.
- Colchicine is the second choice of drug. It is highly effective at a dose of 1.0 mg stat followed by 0.5 mg hourly till symptoms subside or GI side effects (vomiting and diarrhoea) occur or a total of 4 mg of colchicine has been given. To avoid toxic effects, another regimen is 1 mg stat followed by 0.5 mg two to three times a day.
- If patient does not tolerate NSAIDs or colchicine, intra-articular corticosteroids may be tried if a medium or large joint is involved.
- In patients with polyarticular involvement not responding to NSAIDs or colchicine, prednisolone 20–30 mg/day with tapering over 7–10 days is effective.
- Drug therapy for lowering uric acid may be started during an acute attack if effective anti-inflammatory management has been instituted.

Prophylaxis

- Avoidance of alcohol.
- Avoidance of meat and seafood. However, consumption of oatmeal and purine-rich vegetables (for example, peas, beans, lentils, spinach, mushrooms and cauliflower) does not produce increased risk of gout.
- Controlled weight reduction in obese patients.
- Avoiding use of thiazides or loop diuretics, calcineurin inhibitors and niacin.

Drugs for Prophylaxis

- 62% of patients experience a second episode within 1 year, 78% within 2 years, while 7% have no further episode for 10 years even without antihyperuricaemic drugs.
- Antihyperuricaemic drugs are therefore appropriate under following circumstances:
  - Frequent episodes.
  - Chronic tophaceous gout.
  - Radiological erosions.
  - Urate calculi.
  - Asymptomatic patients with urinary urate excretion >1100 mg/24 hours (there is a 50% chance of developing renal calculi in these patients).
  - Persistently raised serum urate (>13 mg/dL in males and >10 mg/dL in females) as there is high risk of urate nephropathy.
- Goal of prophylactic therapy is to lower uric acid to below 6 mg/dL.
- Allopurinol reduces uric acid production through competitive inhibition of xanthine oxidase, which converts xanthine and hypoxanthine to uric acid. Its dose is 300–900 mg daily.
- Febuxostat, a non-purine selective inhibitor of xanthine oxidase, is a new urate lowering drug that is possibly superior to allopurinol. Dose is 40–120 mg/day.
- Uricosuric agents like probenecid and sulphinpyrazone are indicated in selected cases (when uric acid excretion in the urine is below 600 mg/day). Uricosuric drugs are risky if urinary urate excretion is already >800 mg/24 hours. These are contraindicated in those with urate calculi. Uricosurics are ineffective in renal impairment (creatinine clearance <50 mL/minute).
- Uricase is an enzyme which converts uric acid into soluble allantoin. Pegloticase, a polyethylene-glycolated modified porcine recombinant uricase may be used in chronic gout refractory to conventional treatments. Rasburicase, another uricase is approved for use in preventing tumour lysis syndrome.

Q. Describe pseudogout; calcium pyrophosphate dihydrate (CPPD) deposition disease; pyrophosphate arthropathy.

- In this disease, CPPD crystal deposition occurs in fibrous and articular cartilage. Release of CPPD crystals into the joint space provokes an acute attack of synovitis—"pseudogout".
- Conditions associated with CPPD include primary hyperparathyroidism, haemochromatosis, chronic tophaceous gout and others.
- Mostly asymptomatic; identified as an incidental finding on radiographs.
- The knee is the most frequently affected joint. Other sites include wrist, shoulder, ankle, elbow and hands. Acute attacks of pseudogout may be precipitated by trauma, joint surgery, sprain or even a long walk.
- Chronic pyrophosphate arthropathy resembles osteoarthritis involving knees, wrists, metacarpophalangeal joints (particularly second and third), shoulders and hips.

Diagnosis

- Radiographs of joints may show chondrocalcinosis calcification of articular fibro or hyaline cartilage that occurs due to CPPD.
- Ultrasound may be more sensitive than plain radiography of joints in picking up CPPD deposition.
- CPPD crystals can be demonstrated in synovial fluid or articular tissue by polarising microscopy. They are seen as rod- or rhomboid-shaped weakly positive birefringent crystals.

Treatment

- Various treatment modalities are joint aspiration, NSAIDs, intra-articular corticosteroids and colchicine.

Chapter 10

Acute Poisoning and Environmental Emergencies

Q. Describe briefly management of a patient who has ingested a poison.

Q. What are antidotes?

- Kerosene oil poisoning is the most common poisoning in children, while in adults, pesticides, particularly insecticides (organophosphates and carbamates) and aluminium phosphide (ALP) are most often involved in poisoning.
- Management requires five complementary steps. Besides the first step, other steps follow concurrently and not sequentially. These are:
  - Resuscitation and initial stabilisation.
  - Diagnosis of type of poison by history, examination and laboratory investigations.
  - Non-specific therapy to reduce the levels of toxin in the body.
  - Specific therapy to reduce the toxic effects on the body.
  - Supportive care to support the functions of vital organs.
- An additional step in case of external exposure is to remove the patient from the site of exposure and decontaminate after removing clothes.

Resuscitation and Initial Stabilisation

- The initial priorities are the maintenance of airway, breathing and circulation.
- Airway should be secured early in case of caustic ingestion.
- Breathing may require assistance in presence of hypoventilation or acute respiratory distress syndrome.
- Hypotension should be treated with crystalloids first as it is most often due to loss of fluids or toxin-induced vasodilatation. Be careful in patients who have ingested beta-blockers or calcium channel blockers as these agents have negative inotropic effect on myocardium and infusing lot of fluids may precipitate heart failure.
- Before infusing fluids, blood should be collected for investigations including sugar, urea, electrolytes and acid–base status and toxicological investigations.
- Rectal temperature should be obtained in all patients with altered sensorium.
- After initial resuscitation, administer a "cocktail" of 50% dextrose (100 mL), naloxone (0.1–2 mg stat) and thiamine (100 mg) to all patients with altered sensorium. However, if blood glucose can be estimated using a bedside method, dextrose should be infused only if the blood glucose is below 80 mg/dL.
- In view of possibility of precipitating withdrawal reaction naloxone is generally given in a dose of 0.1 mg initially unless the patient has respiratory depression when a loading dose of 2 mg is justified. If there is no response to 0.1 mg and there is no feature of opioid withdrawal, the dose is increased to 2 mg that is given every 2–3 minutes for a total of 10 mg.
- Flumazenil, a benzodiazepine antagonist, is not recommended for empiric use in patients with altered level of consciousness.

Diagnosis of Type of Toxin

- This is based on history, examination and simple laboratory investigations.

Toxidromes

- Based on history and examination findings, it may be possible to define a syndrome associated with certain poisons. This is known as toxidrome.

Toxidrome	Clinical features	Examples
• Cholinergic	DUMBELS: Diarrhoea; urinary incontinence; miosis; bradycardia, bronchorrhea and bronchospasm; emesis; lacrimation, low blood pressure; salivation and sweating. Others include abdominal cramps, hypertension, fasciculations, muscle weakness, confusion, coma, seizures	Carbamates and organophosphates, nicotine

Toxidrome	Clinical features	Examples
• Anticholinergic	Dry flushed skin, dry mucous membranes, urine retention, reduced bowel sounds, abnormal movements, picking at objects, mydriasis, hypertension, tachycardia, hyperthermia, hallucinations, delirium	Datura, antidepressants, antihistamines, phenothiazines
• Narcotic	Miosis, CNS depression, coma, bradycardia, hypothermia, respiratory depression	Opiates
• Sympathomimetic	Sweating, tremors, tachycardia, hypertension, hyperthermia, mydriasis, tachypnoea, agitation, hyperalert, seizures	Amphetamines, cocaine, ephedrine, theophylline, caffeine
• Sedative-hypnotic	CNS depression, confusion, stupor, coma, bradycardia, hypotension, hypopnoea, miosis, hyporeflexia	Barbiturates, benzodiazepines
• Hallucinogenic	Hallucinations, depersonalisation, agitation, hyperthermia, tachycardia, hypertension, nystagmus, mydriasis	Phencyclidine, LSD

Simple Laboratory Tests

- Colour of urine. A pinkish colour of urine occurs in phenothiazines intoxication as well as in myoglobinuria and haemoglobinuria.
- Colour of blood. Chocolate-coloured blood is indicative of methaemoglobinaemia.
- Crystals in urine (in ethylene glycol poisoning).
- Ketonuria (in salicylate poisoning).
- Anion gap (increased in alcoholic ketosis, methanol, ethylene glycol, theophylline, salicylate poisoning and reduced in lithium poisoning).
- Osmolol gap is the difference between the measured osmolality and calculated osmolality and is normally <10 mOsm/kg. Osmolol gap is elevated in patients with ethanol, methanol and ethylene glycol poisoning. Calculated osmolality is derived as: Calculated osmolality $= 2 \times Na^+ +$ Serum glucose (mg/dL)/18 + Blood urea nitrogen (mg/dL)/2.8.

Non-Specific Treatment

- Removal of unabsorbed poison from the gut (gut decontamination) and increasing the excretion of absorbed poison from the body.
- Gut decontamination includes induction of emesis, gastric lavage, use of activated charcoal and cathartics, and whole bowel irrigation.
- Gastric emptying includes induction of emesis and gastric lavage.

Removing Unabsorbed Poison from Gut

- Before performing a procedure for gastric emptying, consider:
  - Whether the ingestion is potentially dangerous?
  - Can the procedure remove a significant amount of toxin?
  - Whether the benefits of a procedure outweigh its risks?
- If the patient has ingested a non-toxic agent, non-toxic dose of a toxic agent, or if he is free of symptoms despite passage of time during which the toxin is known to produce features of toxicity, do not perform a gut decontamination procedure.
- Gastric emptying is also not indicated if the patient had prior repeated vomiting, the toxin is absorbed rapidly or the patient presents late after ingestion.
- If the risks of a procedure outweigh the possible benefits, gastric emptying should be avoided (e.g. ingestion of volatile hydrocarbons, caustics).
- If the patient has ingested a high-risk toxin (cyanide, paracetamol), gastric emptying is indicated even if he is asymptomatic.

Syrup of Ipecac

- Syrup of ipecac is used to induce emesis with the intention to remove the poison from the stomach. Vomiting occurs within 30 minutes of ingestion of ipecac.
- Ipecac may be used in an alert conscious patient who has ingested a potentially toxic amount of a poison within the last 1 hour.

- It should be avoided in:
  - comatose patients
  - patients with seizures
  - patients likely to deteriorate rapidly
  - Patients who have ingested hydrocarbons or corrosives.
- However, at present, it is rarely used.

Gastric Lavage

- For orogastric lavage, the patient should be in a left lateral position with the head lower than the feet, so as to avoid aspiration. If a patient is unconscious intubate the patient before passing a lavage tube.
- Gastric lavage may be considered in a patient who has ingested a potentially life-threatening amount of a toxic agent within the last 60 minutes. It may also be used within 2–4 hours of ingestion of chemical poisons but its utility in such situations has not been proven.
- Lavage is contraindicated following ingestion of strong caustics, non-toxic agents and volatile hydrocarbons.

Cathartics

- Commonly used cathartics are magnesium sulphate, sorbitol and magnesium citrate.
- Repetitive doses of these agents should be avoided.
- There is no data to support their efficacy and their use is not recommended at present.

Activated Charcoal

- Activated charcoal has enormous surface area and can adsorb large amounts of chemicals.
- The usual dose is 1 g/kg body weight or 10 parts of charcoal for every 1 part of toxin, whichever is greater.
- Activated charcoal is contraindicated in patients with unprotected airway and caustic ingestion.
- Activated charcoal is not effective in adsorbing lithium, iron, DDT, methanol, ethanol, metals and hydrocarbons.
- It is likely to be beneficial if a patient has ingested a potentially toxic amount of a poison within 60 minutes of presentation.

Whole Bowel Irrigation

- For whole bowel irrigation, isotonic solution of polyethylene glycol-electrolytes in a dose of 2 L/hour is used orally for 4–6 hours or till the rectal effluent is clear.
- The components of this solution are not absorbed through the intestines; instead, it flushes the gut mechanically.
- At present, there are no established indications for the use of whole bowel irrigation.
- It is an option for potentially toxic ingestions of sustained-release drugs, enteric-coated drugs, iron and drug packets.
- It is contraindicated in patients with bowel obstruction, perforation, ileus and in patients with haemodynamic instability or compromised unprotected airways.

Enhancement of Excretion of Toxin

- Important methods for enhancing excretion are forced diuresis, alteration in urinary pH, multiple doses of charcoal, peritoneal and haemodialysis, haemoperfusion, haemofiltration and exchange transfusion.

Forced Diuresis

- Infusing large amount of intravenous fluids in order to possibly increase toxin excretion is not recommended at present and should not be practiced.

Urine Alkalinisation

- Urinary alkalinisation is useful in salicylates, phenobarbital and lithium intoxication.
- For this, 5% dextrose containing 20–35 mEq/L of bicarbonate is infused at a rate so as to produce a urine pH 7.5–8.5. To prevent hypokalaemia, add potassium in every second or third bottle.
- Diuresis is not required in most cases (except 2,4-D poisoning) as simple urinary alkalinisation is sufficient to enhance excretion of these toxins. Hence, alkaline diuresis is also not recommended in the management of poisoning.
- During alkalinisation, monitor vitals of the patient along with input/output, electrolytes and acid–base status.
- It is contraindicated in patients with shock, hypotension, renal failure and congestive heart failure.

Multiple-Dose Activated Charcoal (MDAC)

- When multiple doses of activated charcoal are administered, free charcoal remains in the intestines to bind any toxin that has significant enterohepatic circulation.

- Free toxin in the blood also tends to diffuse out of the blood into the intestines where it binds the charcoal, thereby maintaining the concentration of free toxin in the intestines near zero (gastrointestinal dialysis).
- Depending upon the severity of poisoning the doses are: 0.5–1 g/kg body weight every 1–4 hours.
- Indications:
  - May be useful in patients with ingestion of carbamazepine, dapsone, phenobarbital, quinine and theophylline.
  - Data regarding use in digoxin, amitriptyline, salicylate and dextropropoxyphene poisoning is insufficient.

Dialysis

- Peritoneal and haemodialysis are useful in:
  - Poisoning with water-soluble compounds of low molecular weight.
  - Toxin with low volume of distribution.
  - Toxin with low serum protein binding.
  - Toxin not irreversibly bound to the tissues.
- Dialysis is useful in ethanol, methanol, salicylates, theophylline, ethylene glycol, phenobarbital and lithium intoxications.

Specific Therapy

- If the toxin can be identified, administer specific therapy using antidotes. However, antidotes are available for a few toxins only.

Antidotes

Antidotes	Poison
- Atropine	Cholinesterase inhibitors (organophosphates, carbamates)
- 2-PAM	Organophosphates
- Naloxone	Opioids
- Dextrose	Hypoglycaemic agents
- Sodium bicarbonate	Tricyclic antidepressants
- Methylene blue	Methaemoglobinaemia-producing agents
- Ethanol	Methanol, ethylene glycol
- Snake antivenin	Snake bites
- Deferrioxamine	Iron
- BAL (Dimercaprol)	Lead, arsenic, mercury
- CaNa$_2$EDTA (Edetate)	Lead
- D-penicillamine	Mercury, lead, arsenic
- 2,3-dimercapto-succinic acid	Lead, mercury, arsenic
- Fomepizole (4-MP)	Methanol, ethylene glycol
- N-acetylcysteine	Paracetamol
- Flumazenil	Benzodiazepines
- Glucagon	β-blockers, calcium channel blockers
- Cyanide kit	Cyanide

Supportive Therapy

- As antidotes are available only for a few toxins, the treatment of most of the cases with poisoning is largely supportive.
- The aim of the supportive treatment is to preserve the vital organ functions till poison is eliminated from the body and the patient resumes normal physiological functions.
- Therefore, support the functions of central nervous system, cardiopulmonary system and renal system with proper care for coma, seizures, hypotension, arrhythmias, hypoxia and acute renal failure.
- Monitor the fluid, electrolyte and acid–base status closely.

Q. What are the commonly encountered poisonous snakes in your place? Discuss the clinical manifestations, diagnosis and management of snake bites.

- The poisonous snakes belong to five families or subfamilies.

Family	Common varieties
• Elapidae	Cobras, kraits, mambas, coral snakes
• Viperidae	Russell's viper, *Echis carinatus* (saw-scaled viper)
• Colubridae	Boomslangs, bird snakes
• Crotalidae	Pit vipers, hump-nosed viper, bush master
• Hydrophidae	Sea snakes

- In India, the most important species are cobra (*Naja naja*), common krait (*Bungarus caeruleus*), Russell's viper, *E. carinatus* (saw-scaled viper) and hump-nosed viper.

Snake Venoms

- Venoms are secreted by salivary glands and the duct of glands open well above the tip of fangs. Due to this reason a snake may not be able to inject venom even after biting a victim.
- The venom of a given species is usually predominantly neurotoxic (e.g. cobras, kraits and Russell's viper), or necrotising and haematotoxic (e.g. vipers).
- The neurotoxins of Elapidae are rapidly absorbed into bloodstream, whereas the Viperidae venom is taken up more slowly through lymphatics.
- Various components of venoms include the following:
  - Pro-coagulant enzymes are major factor in viper venom. These stimulate blood clotting and consumption of fibrinogen as a result of disseminated intravascular coagulation (DIC) resulting in incoagulable blood.
  - Haemorrhagins are zinc metalloproteinases that damage the endothelial lining of the blood vessels causing spontaneous systemic bleeding.
  - Cytolytic or necrotic toxins damage cell membranes resulting in increased permeability. This leads to local swelling and gangrene of bitten part.
  - Haemolytic and myolytic phospholipases A2 enzymes damage cell membranes, endothelium, skeletal muscle, nerve and red blood cells.
  - Pre-synaptic neurotoxins or β-bungarotoxins are phospholipases A2 that interfere with release of acetylcholine. These toxins are present in venoms of kraits and Russell's viper.
  - Post-synaptic neurotoxins or α-bungarotoxins are polypeptides that compete with acetylcholine at the neuromuscular junctions producing curare-like paralysis. Both cobra and krait venoms have these toxins.

Clinical Manifestations

Bites by Elapidae (cobras, kraits)

- In general, elapid venoms are best known for their neurotoxic effects.
- Local pain and swelling are frequent in cobra bites. Krait bites are painless and without any local swelling.
- Early symptoms are vomiting, abdominal pain (in krait bite), "heaviness" of eyelids, blurred vision, diplopia, paraesthesiae around the mouth, hyperacusis, headache, dizziness, vertigo, hypersalivation, red eyes and "gooseflesh".
- Paralysis is first detectable as ptosis and external ophthalmoplegia. Later, the palate, jaws, tongue, vocal cords, neck muscles and muscles of deglutition become paralysed.
- Respiratory failure may be precipitated by paralysis of intercostal muscles and diaphragm.
- Patients "spat" at by spitting cobras may develop venom ophthalmia.
- Cobra bites may also produce cardiovascular involvement producing hypotension and ECG changes.

Bites by Viperidae (vipers)

- In general, the Viperidae venoms are best known for their severe local manifestations and haematotoxic effects.
- There is local swelling, which spreads rapidly and may involve the whole limb and adjacent trunk.
- Bruising, blistering, and necrosis are very common. Necrosis is particularly common if the envenomation occurs in tight fascial compartments like digits and anterior tibial compartment.
- Haemostatic abnormalities are characteristic. These include persistent bleeding from fang puncture site and venepuncture sites. Spontaneous bleeding is most often detected in the gingival sulci. In addition, epistaxis, haematemesis, cutaneous bleeding, haemoptysis and subconjunctival, retroperitoneal and intracranial haemorrhages can occur.
- Hypotension and shock occur very frequently.
- Direct myocardial involvement is suggested by abnormal ECG or arrhythmias.

- Acute renal failure can occur with Russell's viper, hump-nosed viper and sea snake envenomation. It usually becomes clinically evident by 7 days. Various causes include shock, myoglobinuria, haemolytic-uraemic syndrome, direct toxic effect and haemolysis.
- Besides local and haemotoxic features, Russell's viper also produces renal failure and neuroparalysis. Acute pituitary failure can also occur.

Bites by Hydrophidae (sea snakes)

- Sea snakes produce myotoxicity that produces muscle pains, muscle weakness and rhabdomyolysis producing myoglobinuria. Cardiac involvement can occur due to release of potassium (hyperkalaemia) from necrosed muscles.
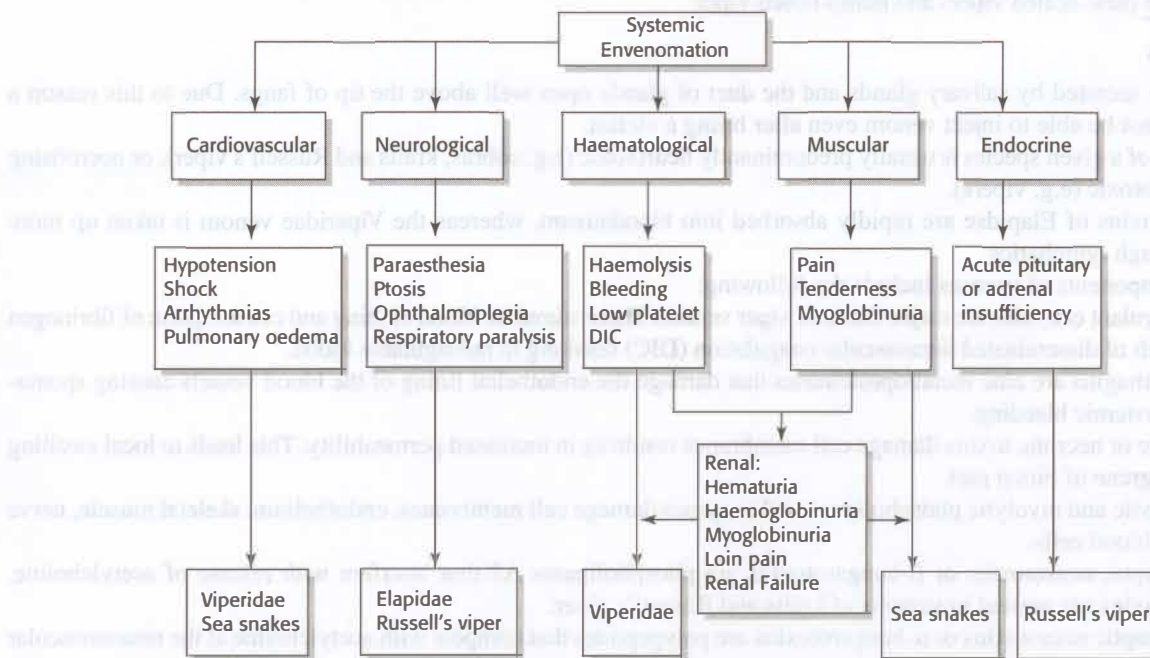
Investigations
- Total leucocyte count exceeding 20,000/mm^3 indicates severe envenomation.
- Anaemia results from bleeding and rarely haemolysis.
- Thrombocytopenia in viper bites.
- Pink plasma and black urine indicate intravascular haemolysis.
- Urine should be examined for red blood cells, red cell casts, protein and myoglobin.
- Twenty minute whole blood clotting test and clot quality test are useful. Incoagulable blood at 20 minutes indicates systemic envenomation. The size of the clot is roughly proportional to the fibrinogen concentration.
- Whole blood or plasma prothrombin time, and tests to detect fibrin degradation products (FDPs).
- Renal function should be assessed by blood urea, serum creatinine and electrolytes.
- Electrocardiogram may show sinus bradycardia, ST–T changes and various degrees of AV blocks.
- Creatine phosphokinase (CPK) is elevated in sea snake bites.
- Specific snake venom antigens may be detected in wound aspirates and body fluids.

Management
- Indian Snake Bite Protocol gives guidelines on managing a patient with snake bite.

First Aid
- Follow the do it "RIGHT" approach.
  - *R*eassure the patient.
  - *I*mmobilise the bitten limb. This reduces absorption of venom.
  - *G*et to the nearest *H*ospital.
  - *T*ell the doctor about the symptoms.
- Application of tourniquet is controversial. It may be used in case of cobra or krait bite if the facilities for administration of antivenom are more than 30–60 minutes away from the location where the patient has been bitten. The tourniquet should be

at least 1–1.5 cm wide. It should be applied 5–10 cm proximal to swelling/bite area. It should be loose enough to allow one finger to pass beneath without any difficulty. The purpose is to impede lymph flow and not blood flow. However, it may be difficult to identify the snake in the field setting and therefore tourniquet is not recommended in the Indian protocol.

- Local incision is not advisable.
- Do not apply ice locally for relieving the pain as it can damage the exposed nerves and vessels.
- The level of swelling should be marked on the skin, every 15 minutes.
- If the snake has been killed, handle the dead snake carefully as there is a risk of a second bite. Decapitated snake heads can "bite" up to 1 hour after death of snake due to reflex action.

Hospital Treatment

- Maintain circulation, airway and breathing.
- Clean the site of bite and elevate it to reduce local oedema.
- Send blood for various investigations.
- Examine the patient to look for features of envenomation.
  - Extent of local swelling and local oozing of blood.
  - Evidence of compartment syndrome (local tenseness, tenderness, absence of pulsation and muscle weakness).
  - Examine for enlarged and tender lymph nodes draining the limb.
  - Check blood pressure in both supine and standing positions.
  - Assess the pulse rate and respiratory rate.
  - Examine skin and mucous membranes for any evidence of bleeding. The earliest evidence of bleeding may be in the form of gum bleeding and therefore always examine the oral cavity.
  - Examine nervous system for any signs of toxicity.
  - Single breath count can be used to assess the strength of respiratory muscles.

Antivenom Treatment

- The general indications for antivenom are given in the box.

Indications for Antivenom

Signs of systemic envenomation as indicated by:
- Impaired consciousness
- Neurotoxicity
- Hypotension and shock, abnormal ECG and other evidences of cardiovascular dysfunction
- Haemostatic abnormalities such as spontaneous systemic bleeding and evidence of coagulopathy
- Generalised rhabdomyolysis
- Evidences of intravascular haemolysis
- Evidences of renal failure such as oliguria, uraemia, raised serum creatinine, hyperkalaemia, etc.

Signs of local envenomation occurring in the first 4 hours as indicated by:
- Local swelling involving more than half of the bitten limb
- Extensive blistering and bruising
- Rapid spread of local swelling
- Painful enlargement of lymph nodes draining bitten limb

- Monospecific (monovalent) antivenom is ideal if the biting species is known. However, it is not available in India.
- Polyspecific (polyvalent) antivenom available in India is effective against the four common varieties of snakes, i.e. cobra, krait, Russell's viper and saw-scaled viper. It is ineffective against hump-nosed viper. It is prepared from the equines hyperimmunised with venom.
- Skin sensitivity test is unreliable and is therefore not recommended.
- Required dose of antivenin is added in normal saline and the infusion begins at a rate of 1 mL/minute in the beginning. If no reaction occurs, the total quantity is infused rapidly over 1 hour. Keep epinephrine loaded to treat any reaction to antivenin.
- Dose is 60–100 mL of antisnake venom (ASV) and is same for both children and adults. In the case of haemotoxic bites a repeat ASV dose is indicated if the bleeding continues after 6 hours or the whole blood clotting time is still more than 20 minutes. This is because liver requires 6 hours to restore clotting factors and additional ASV before this period is not required. A third dose may be required after another six hours in some cases.

- For neurotoxic features, a repeat dose is indicated if neurological features persist or worsen after 1–2 hours.
- Antivenom can cause two types of reactions, an early (anaphylactoid) reaction and a late (serum sickness type) reaction. The early (anaphylactoid) reaction is characterised by itching, urticaria, cough, nausea, vomiting, fever and tachycardia. Some may develop systemic anaphylaxis with hypotension, bronchospasm and angioneurotic oedema. This is treated with adrenaline 0.5–1.0 mL subcutaneously (may be repeated), chlorpheniramine maleate 10 mg intravenously and hydrocortisone 100 mg intravenously.

Cholinergics

- Cholinergic agents are useful in patients with neurotoxic features, particularly cobra bite.
- Neostigmine in a dose of 0.5 mg is administered intravenously for every 30 minutes to 4 hours along with atropine (to reduce cholinergic effects of neostigmine).

Supportive Therapy

- Respiratory paralysis should be treated by artificial ventilation.
- Hypotension and shock should be treated with fresh whole blood or fresh frozen plasma, dopamine and hydrocortisone.
- Oliguria and renal failure should be treated conservatively, failing which dialysis should be done.
- Local infection should be prevented by antibiotics covering Gram-negative organisms and anaerobes. All patients should receive antitetanus prophylaxis.
- At a later stage, some patients may require surgical debridement, skin grafting or fasciotomy.
- Haemostatic disturbances should be treated with fresh whole blood or fresh frozen plasma, cryoprecipitates or platelet concentrates.

DO NOTs in snake bite

- Local incision and suction of wound
- Application of ice packs and potassium permanganate
- Application of tight constriction bands impeding arterial flow
- Infiltration of antivenom locally

Q. Explain toxicity caused by scorpion stings.

- The poisonous scorpions of India include the red scorpion (*Mesobuthus*) and the black scorpion (*Palamnaeus*).
- The glands in the terminal segment of the tail produce venom that is injected by a stinger.

Clinical Features

- Most stings are minor. The clinical features of envenomation develop within 2–12 hours of sting by a poisonous scorpion.

Local Features

- Sting may be followed by the onset of intense pain at the site within several minutes. Often there is intense pain with mild palpation or tapping over the site (the "tap test"). Pain or numbness may radiate up the extremity.

Systemic Features

- Systemic features reflect sympathetic, parasympathetic and neuromuscular excitation.
- Initial features are due to transient cholinergic hyperactivity. This produces restlessness, anxiety, vomiting, profuse sweating, salivation, sensation of tongue thickening, dysphagia, bradycardia, hypotension and priapism.
- These are followed by sustained adrenergic hyperactivity resulting in hypertension, tachycardia, chest discomfort, cold extremities and myocardial failure. Hypertension occurs within 6 hours of sting while pulmonary oedema occurs in 2–56 hours after being stung.
- In late stages, hypotension and shock develop.
- Electrocardiographic features suggestive of myocarditis may be present.

Management

- Mild analgesics for relieving pain.
- Tetanus vaccine according the immune status of the patient.
- Monitor for cardiac rhythm, conduction disturbances and oxygen saturation.
- If signs of respiratory failure occur, intubate the patient.
- Correction of fluid deficit; avoid large amount of fluids without proper monitoring because of the risk of pulmonary oedema.

- Prazosin (0.25–0.5 mg every 4–6 hours) to control hypertension. It is an antidote for scorpion stings. An alternative is to give nifedipine; however, it should be avoided in the presence of tachycardia and impending congestive heart failure.
- Dopamine infusion for hypotension.
- Prazosin and furosemide to control pulmonary oedema associated with normal or high blood pressure.
- Glucose–insulin infusion may be beneficial in systemic envenomation.
- Role of serotherapy (use of scorpion antivenin) is controversial.

Q. Discuss the clinical manifestations, diagnosis and management of organophosphorus and carbamate poisoning.

- Most common cause of acute poisoning in India.
- Common organophosphorus compounds are malathion, parathion, dichlorvos, diazinon and chlorothion. These compounds irreversibly inhibit acetylcholinesterase and cause accumulation of acetylcholine at muscarinic and nicotinic synapses.
- Common carbamate insecticides include carbaryl, aldicarb and propoxur. These compounds reversibly inhibit acetylcholinesterase and cause accumulation of acetylcholine at neurosynapses.

Clinical Features

- Organophosphorus compounds produce muscarinic, nicotinic and CNS effects. Carbamates produce a similar clinical picture, but of shorter duration and lower order of toxicity.

Muscarinic Manifestations

- DUMBELS (refer previously).
- Nausea, vomiting, abdominal pain and faecal incontinence.
- Increased bronchial secretions, cough and occasionally pulmonary oedema.
- Excessive sweating, salivation and lacrimation.
- Blurring of vision and miosis.
- Increased urinary frequency and incontinence.
- Bradycardia, hypotension and conduction blocks.

Nicotinic Manifestations

- Twitching, fasciculations, weakness, diminished respiratory effort, hypertension and tachycardia.

CNS Manifestations

- Anxiety, restlessness, tremors, convulsions, confusion, weakness and coma.

Intermediate Syndrome

- Syndrome of muscular paralysis occurs within 24–96 hours after ingestion of an organophosphate and following treatment of acute cholinergic syndrome.
- Muscle weakness affects predominantly neck flexors, proximal limb muscles, those supplied by cranial nerves and respiratory muscles.

Organophosphate-Induced Delayed Polyneuropathy (OPIDN)

- Cramping muscle pain in the lower limbs, distal numbness and paraesthesiae followed by progressive weakness, depression of deep tendon reflexes in the lower limbs and in severe cases, in the upper limbs.

Diagnosis

- Diagnosis of organophosphorus poisoning can be confirmed by demonstrating a reduction of cholinesterase activity in plasma or in red blood cells, to less than 50% of normal.
- With carbamates reduction of cholinesterase level is rare because of the rapid reversibility of inhibition.

Management

General Measures

- Remove the patient from site of exposure and wash the skin with soap and water.
- In the case of ingestion, gastric lavage should be done if the patient presents within first one hour of ingestion.
- Activated charcoal is given orally at a dose of 1–2 g/kg body weight.

- Meticulous care of the airway along with oxygenation is important. If there is respiratory insufficiency, patient should be ventilated.
- Benzodiazepines for convulsions. They also reduce morbidity and mortality even in the absence of convulsions.

Specific Measures

Atropine

- Atropine is the main antidote. If the initial assessment reveals significant cholinergic features (miosis, excessive sweating, poor air entry due to bronchorrhoea and bronchospasm, bradycardia and hypotension) then atropine is required.
- Atropine is administered at a dose of 1.8–3.0 mg intravenously. Five minutes after giving atropine, check the five markers of cholinergic poisoning. A uniform improvement in most of the five parameters is required and not the improvement in just one.
- If after 5 minutes a consistent improvement across the five parameters has not occurred then more atropine is required. Double the dose of atropine every time and continue to double each time when there is no adequate response.
- Target end points for atropine therapy (atropinisation) are: Clear chest on auscultation with no wheeze, heart rate >80 beats/minute, pupils no longer pinpoint, dry axillae and systolic blood pressure >90 mmHg. Pupil size and heart rate alone should not be used as end points.
- Once atropinised set up an infusion of atropine at an hourly dose of 10–20% of the total dose of atropine given initially. Review every 15 minutes to see whether the atropine infusion rate is adequate. Further boluses may be given if required.

Pralidoxime (2-PAM)

- Pralidoxime (2-PAM) is a cholinesterase reactivator. It is effective for nicotinic as well as muscarinic features of toxicity.
- The usual dose is 30 mg/kg initially over 20 minutes followed by a constant infusion at 9 mg/kg/ hour. It is usually continued for 12–24 hours after atropine is no longer required.
- The role of PAM in carbamate poisoning is controversial. It should be avoided in carbaryl ingestion. It may be used in severe carbamate poisoning or in those who present after ingestion of an unknown cholinesterase inhibitor.

Q. Describe the toxicity caused by aluminium phosphide poisoning.

- Aluminium phosphide (ALP), a solid fumigant widely used as a grain preservative, was the leading cause of suicidal poisoning in north India in the last decade.

Mechanism of Toxicity

- After ingestion, phosphine is liberated in the stomach that is absorbed into the circulation.
- Phosphine is a protoplasmic poison that inhibits various enzymes and protein synthesis. It is a potent respiratory chain enzyme inhibitor that produces widespread cellular hypoxia due to inhibition of cytochrome oxidase.
- Inhibition of cytochrome oxidase results in generation of free oxygen radicals or superoxide that stimulates superoxide dismutase.

Clinical Features

- The fatal dose of an unexposed pellet of ALP is 150–500 mg.
- Clinical manifestations develop within 30 minutes of ingestion.
- Initial features include retrosternal burning, epigastric discomfort and recurrent vomiting and diarrhoea. There is fishy smell from breath.
- Within next 6–8 hours patients develop systemic features most prominently related to cardiovascular and respiratory systems.

Cardiovascular Features

- Important cardiovascular features are hypotension, shock, tachycardia or bradycardia and arrhythmias.
- Shock occurs because of cardiotoxicity, recurrent vomiting and widespread vascular injury.
- A few patients may develop congestive heart failure due to myocardial depression.
- The ECG changes include arrhythmias, intraventricular conduction blocks, ST depression and T inversion, ST elevation and various blocks.

Respiratory Features

- The respiratory features include cough, dyspnoea, cyanosis, pulmonary oedema and ARDS that usually occur after 6–36 hours of ingestion.

Metabolic Features

- Hypo- or hypermagnesaemia and metabolic acidosis are common.

Miscellaneous

- Other features include liver damage indicated by elevated transaminases and bilirubin, renal failure and pericarditis.

Diagnosis

- Diagnosis of ALP poisoning is made by typical features of poisoning along with fishy smell in the breath and vomitus.
- Confirmation can be done by silver nitrate test on lavage fluid or on breath.

Management

- If patient presents early after ingesting ALP, perform a gastric lavage using potassium permanganate in 1:10,000 dilution. It oxidises phosphine to non-toxic phosphates.
- Activated charcoal also adsorbs phosphine.
- Adequate ventilation and urine output help to maintain adequate excretion of phosphine.
- Supportive care is the most important step in the management.
  - Monitor the central venous pressure and if possible, the pulmonary arterial wedge pressure.
  - Infuse large volumes of saline to maintain the systolic pressure above 90 mmHg. Four to six litres of saline may be required in the first few hours.
  - Infuse large doses of intravenous bicarbonate to correct acidosis that is quite severe in most cases.
  - Initiate norepinephrine or dopamine if blood pressure is not maintained with saline.
  - If required, add dobutamine.
- Role of magnesium sulphate in reducing toxicity of phosphine remains controversial but most clinicians use it.

Q. Explain barbiturate poisoning.

- Barbiturates are classified into long-acting and short-acting barbiturates. Phenobarbital, a long-acting barbiturate, was commonly implicated in suicidal attempts during 1960–1980. However, it is uncommon at present. It is a weak acid.

Clinical Features

- In large overdose, there is CNS depression ranging from lethargy to coma, hypotension, pulmonary oedema and cardiac arrest. In addition, it causes hypothermia and ventilatory depression. Pupils are usually constricted, but may dilate in terminal phases. Bullous skin lesions may be seen with severe overdose.
- With phenobarbital, signs of toxicity usually appear when serum concentration exceeds 4 mg/dL.

Management

- Prompt gastrointestinal decontamination should be done by lavage. Repeated oral administration of activated charcoal 2-4 hourly is very effective.
- General measures with particular emphasis on respiratory and cardiovascular support, and correction of temperature and electrolyte derangements.
- Alkalinisation of urine (without diuresis) is effective in phenobarbital poisoning. It enhances renal excretion of phenobarbital.
- Haemodialysis is effective in removing long-acting barbiturates, especially phenobarbital. It is reserved for severely intoxicated patients with high blood levels, exceeding 10–15 mg/dL.

Q. Write a short note on the toxicity caused by methanol poisoning.

- This occurs when industrial spirit (methylated) is consumed, or when the supply of liquor is adulterated with methyl alcohol.
- Methanol is a mild CNS depressant.
- Methanol as such is not a toxic agent. However, its metabolites—formaldehyde and formic acid—are responsible for its toxicity.
- The enzyme responsible for conversion of methanol to formaldehyde is alcohol dehydrogenase while aldehyde dehydrogenase, formaldehyde dehydrogenase and other enzymes convert formaldehyde to formic acid.
- Oxidation of methanol is much slower than that of ethanol. In the presence of both ethanol and methanol, the former is preferentially metabolised by alcohol dehydrogenase resulting in a reduced toxicity of methanol.

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┌─────────────────────────┐
│        Methanol         │
└─────────────────────────┘
            │ Alcohol dehydrogenase
            ▼
┌─────────────────────────┐
│      Formaldehyde       │
└─────────────────────────┘
            │ Aldehyde dehydrogenase
            ▼
┌─────────────────────────┐
│       Formic acid       │
└─────────────────────────┘
            │ Folate
            ▼
┌─────────────────────────┐
│   Carbon dioxide + water│
└─────────────────────────┘
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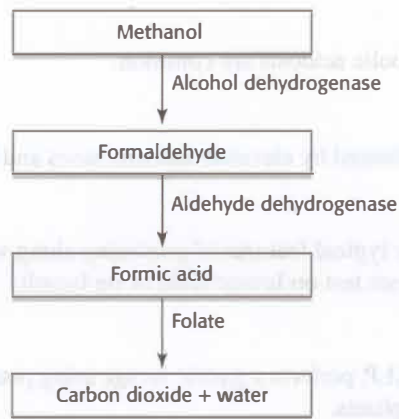
Clinical Features

- Early manifestations are caused by methanol and late manifestations are due to the methanol metabolite formic acid.
- Methanol produces nausea, vomiting, abdominal pain, headache, vertigo, confusion, obtundation, convulsions and coma.
- Late manifestations of formic acid are metabolic acidosis and retinal injury. The ophthalmologic manifestations include clouding and diminished vision, dancing and flashing spots, dilated or fixed pupils, hyperaemia of the optic disc, retinal oedema and blindness.
- Other manifestations are rapid breathing due to metabolic acidosis, myocardial depression, bradycardia, shock and anuria.
- An uncommon complication is putaminal necrosis, which presents with rigidity, tremor, masked faces and monotonous speech.

Diagnosis

- Diagnosis is confirmed by measurement of serum methanol level, which is usually more than 20 mg/dL.
- Methanol-derived formic acidosis can be confirmed by a large anion gap, low serum bicarbonate and elevated serum formate levels.
- The osmolol gap is elevated due to methanol.

Management

- Gastrointestinal decontamination in early stages.
- Correction of systemic acidosis with sodium bicarbonate.
- Ethanol therapy is indicated in patients with visual symptoms or methanol level exceeding 20–30 mg/dL. Ethanol competitively inhibits alcohol dehydrogenase which reduces conversion of methanol to formic acid.
- Haemodialysis is indicated for patients with methanol level exceeding 50 mg/dL, for those with visual signs and for those with metabolic acidosis unresponsive to bicarbonate.
- Another potent antidote of methanol poisoning is 4-methylpyrazole or fomepizole. It is a direct, potent inhibitor of alcohol dehydrogenase and therefore, may be more effective than ethanol, which is a competitive antagonist.
- Folinic acid (leucovorin) is given in addition to ethanol or 4-methylpyrazole. It acts by increasing the rate of degradation of formic acid to carbon dioxide.

Q. What is salicylate poisoning? Explain its management.

- In general, adults are less vulnerable to the toxic effects of salicylates than children. In adults, plasma salicylate level above 50 mg/dL indicate moderate to severe poisoning.
- Oil of Wintergreen is extracted from the leaves of a small evergreen herb. The plant has cherry shaped berries. The leaves contain a very high concentration of methyl salicylate which is a precursor of aspirin. Wintergreen should NEVER be ingested and only used topically in dilutions of 25% or less to limit the transdermal absorption.

Clinical Features

- The earliest signs and symptoms of salicylate toxicity develop within 1 to 2 hours of ingestion and include nausea, vomiting, sweating and tinnitus.

- These are followed by early CNS features like tachypnoea, hyperactivity, agitation, delirium and hallucinations.
- Later the patient may develop coma, seizures and pulmonary edema.
- The initial respiratory alkalosis is followed later by metabolic acidosis. Marked acidosis is regarded as a very serious feature as it may herald sudden respiratory or cardiac arrest.
- A marked increase in body temperature is indicative of severe toxicity.
- Development of respiratory acidosis indicates ARDS.
- Acute poisoning also produces GI symptoms and blood level correlates with toxicity.
- In chronic poisoning, GI features are less severe while CNS features including tinnitus are prominent. Blood levels do not correlate with symptoms in chronic poisoning.
- Hypoglycaemia and hypokalaemia are frequent. Hypokalaemia occurs due to intracellular shift produced by respiratory alkalosis as well as due to increased renal excretion of potassium. Therefore, check glucose and potassium.

Management

- General measures including gastric lavage and activated charcoal.
- Maintain intravascular volume by intravenous fluids.
- Alkalinisation of urine in moderate or severe poisoning.
- Correction of hypoglycaemia and hypokalaemia.
- Peritoneal dialysis or haemodialysis may be required in severe cases.

Q. Describe the toxicity caused by mushroom poisoning.

- Among the many types of mushrooms only a small number are poisonous. In general, mushroom poisoning that has its onset within 3 hours of ingestion is not likely to involve a deadly mushroom.
- Majority of the deaths due to mushroom poisoning result from ingestion of *Amanita phalloides* ("death cap"). It contains two types of toxins, both of which are heat stable and survive cooking:
  1. "Phallotoxins" causing severe gastroenteritis within 6–12 hours of ingestion.
  2. "Amatoxins" causing delayed liver and renal tubular damage.

Management

- The mushroom eaten should be identified, ideally by an expert.
- Toxins have been found in the duodenal aspirate as long as 36 hours after ingestion. Therefore, a gastric lavage may be performed even in late phases of poisoning. Repeated doses of activated charcoal are useful.
- Initial treatment consists of maintenance of fluid and electrolyte balance.
- The value of thioctic acid, a Krebs cycle coenzyme, is doubtful.
- Penicillin and silymarin inhibit uptake of amatoxin by hepatocytes and their use has been associated with reduced morbidity and mortality.
- Otherwise, management is supportive and includes treatment of hepatic and renal failure.

Q. Discuss the clinical features, laboratory features and treatment in case of oleander poisoning.

- Ingestion of yellow oleander (*Thevetia peruviana*) is toxic.
- Oleander plant contains glycosides that resemble digitoxin, a cardiac glycoside. These include thevetins A and B, and neriifolin.
- All parts contain the toxin but the maximum amount is in the seeds.

Clinical Features

- Symptoms of poisoning generally start within 2–3 hours of ingestion.
- Gastrointestinal irritation produces nausea, vomiting, diarrhoea and abdominal pain.
- Other features include dizziness, pupillary dilatation, tingling and numbness, restlessness, bradycardia, arrhythmias, hypotension, nervous system toxicity and abdominal cramps.
- Electrocardiographic features are sinus bradycardia, AV blocks, ST segment depression, inversion of T waves, AV dissociation, ventricular ectopics, and in severe cases, ventricular tachycardia and fibrillation.

Laboratory Features

- Hyperkalaemia and acidosis.
- Estimation of digoxin using radioimmunoassay (cross-reactivity of oleander glycosides with digoxin).

Treatment

- Correction of fluid, electrolyte and acid–base disturbances.
- Gastric emptying.
- Repeated dose of activated charcoal.
- Atropine and pacing for bradycardia-related arrhythmias.
- Lidocaine for ventricular tachyarrhythmias.
- Digoxin-specific Fab antibody fragments in life-threatening oleander poisoning.

Q. Write briefly on datura poisoning, explaining clinical features and management.

- *Datura stramonium* (jimson seed) produces anticholinergic syndrome.
- All the parts of this plant are poisonous but the seeds and fruit are the most toxic.
- The most popular mode of poisoning is by mixing the seeds in sweets and giving to others with the purpose of thefts.
- The active toxic agents include atropine and scopolamine.
- Atropine and related compounds block acetylcholine at the receptor sites of postganglionic synapses of the cholinergic nerves.

Clinical Features

- Symptoms of toxicity usually appear within 30 minutes of ingestion and last for 24–48 hours.
- Classically, in addition to manifesting tachycardia, the features are described as "hot as a hare" (cutaneous vasodilatation), "blind as a bat" (ciliary muscle paralysis, mydriasis), "dry as a bone" (anhidrosis, dryness of mouth, urinary retention, decreased bowel motility), "red as a beet" (cutaneous vasodilatation causing flushing) and "mad as a hatter" (CNS arousal, agitation, delirium, hallucinations).
- The pupils are dilated.
- In fatal cases, stupor, coma and convulsions occur. Death occurs due to respiratory paralysis or cardiovascular collapse.

Management

- Gastric lavage and support of various vital organs.
- Activated charcoal is helpful as it adsorbs the alkaloids.
- Urinary catheterisation.
- Control of hyperthermia.
- Benzodiazepines are effective in the treatment of agitation.
- Role of physostigmine, a cholinesterase inhibitor, is controversial.

Q. What are the common chemical and biological agents used in terrorism.

Common Chemicals that may be used in Terrorism

Asphyxiants	Vesicants
Blood	• Mustard gas
• Hydrogen cyanide	• Lewisite
• Hydrogen sulphide	**Nerve agents**
Choking	• Tabun
• Phosgene	• Sarin
• Chlorine	• Soman
• Sulphur dioxide	• VX
• Nitrogen dioxide	**Tear gases**
	• 2-chloro-1-phenylethanone

Common Biological Agents that may be used in Terrorism

• Anthrax	• Tularaemia
• Smallpox	• Botulism
• Plague	• Viral haemorrhagic fevers

Q. What are the clues to chemical and biological terrorism?

Clues to Chemical Terrorism

- Any unusual increase in the number of people seeking care, especially with respiratory, neurological, dermatological or gastrointestinal symptoms
- Any clustering of symptoms or unusual age distribution (e.g. chemical exposure in children)
- Any unusual clustering of patients in time or location (e.g. persons who attended the same public event; subways)
- Location of release not consistent with a chemical's use
- Simultaneous impact to human, animal and plant populations
- Unprotected rescuers becoming victims themselves

Clues to Bioterrorism

- Single case of a disease caused by an uncommon agent (e.g. smallpox, inhalational or cutaneous anthrax, pneumonic plague)
- Large numbers of persons with similar diseases
- Large number of persons with unexplained deaths
- High morbidity and mortality in association with a common disease
- Failure of patients with a common disease to respond to usual therapy
- Unusual, atypical or genetically engineered strain of an agent
- Agent resistant to most antibiotics
- Disease with an unusual geographic distribution
- Sudden increase in occurrence of a disease, otherwise stable (e.g. plague, tularemia)
- Atypical disease transmission through aerosols or water
- Unusual illness that affects a large population
- Unusual pattern of death or illness among animals
- Simultaneous clusters of similar illness in non-contiguous areas

Q. How will you recognise and treat patients exposed to a chemical terrorist attack?

Agent	Mechanism of toxicity	Clinical features	Examples	Management

• Nerve agents	• Inactivate acetylcholin-esterase (ACh) enzyme, causing muscarinic, nicotinic and CNS effects	• Mild to moderate toxicity
		  • Miosis
		  • Blurred vision
		  • Rhinorrhoea
		  • Headache
		  • Sweating
		  • Vomiting, diarrhoea
		  • Muscle fasciculations
		• Severe toxicity
		  • Additional features include seizures and loss of consciousness
			• Sarin
			• Soman
			• Tabun
			• VX
				• Decontamination
				• Suction and oxygen
				• Atropine
				  • Reverses muscarinic features
				  • 2 mg IV; repeat every
				  • 5 minutes, titrate until effective
				  • IM in the field
				• Pralidoxime (2-PAM)
				  • Re-activates ACh
				  • Reverses nicotinic and muscarinic features
				  • 600–1800 mg IM or 1–2 g IV over 20–30 minutes
				  • Repeated doses as required
				• Diazepam to prevent/control seizures

Agent	Mechanism of toxicity	Clinical features	Examples	Management
• Asphyxiants				

a. Blood asphyxiants	• Bind with iron in cytochrome a_3 preventing intracellular oxygen utilisation	• Mild to moderate toxicity
		   • Giddiness
		   • Palpitations
		   • Dizziness
		   • Nausea, vomiting
		   • Headache
		   • Increase in rate and depth of breathing (hyperventilation)
		   • Drowsiness
		   • Metabolic acidosis
		   • Hypotension
		   • "Pink" skin colour
		 • Severe toxicity
		   • Immediate loss of consciousness, convulsions and death within 1–15 minutes
			• Hydrogen cyanide
			 • Hydrogen sulphide
				• 100% oxygen by face mask
				 • Intubation with 100% FiO_2 if indicated
				 • Amyl nitrite via inhalation, 1 ampoule every 5 minutes
				 • Sodium nitrite (300 mg IV over 5–10 minutes)
				 • Sodium thiosulphate (12.5 g IV)

b. Choking agents	• Acids or acid-forming agents that react with cytoplasmic proteins and destroy cell structure	• Shortness of breath • Chest tightness • Wheezing • Laryngeal spasm • Mucosal and dermal irritation • Pulmonary oedema • ARDS	• Chlorine • Phosgene • Chloropicrin • Nitrogen dioxide • Sulphur dioxide	• Management of secretions • Oxygen • High dose steroids (value controversial) • Treat pulmonary oedema with PEEP* to maintain PO_2 above 60 mmHg
c. Vesicants or blister agents	• Mustard: Forms metabolites that bind to enzymes, proteins and other cellular components • Lewisite: Binds to thiol groups in many enzymes • Phosgene oxime: Mechanism unknown, but corrosive action like strong acids	• Burning, itching or red skin • Prominent tearing and burning of eyes • Shortness of breath • Nausea, vomiting • Skin erythema and blistering • Watery, swollen eyes • Upper airways sloughing with pulmonary oedema	• Mustard • Lewisite • Phosgene oxime	• Mustard and phosgene oxime have no specific antidotes • For lewisite, British anti-Lewisite (BAL or dimercaprol) IM • Thermal burn therapy • Supportive care

*Positive end-expiratory pressure

Q.   How is body temperature maintained?

- Body temperature or the core temperature is dependent on the balance between heat production and heat loss.
- Heat generation occurs due to various exothermic metabolic processes and absorption of heat from the environment. Muscles are important in heat production and shivering can increase the heat production several times.
- Loss of heat from the body occurs in several ways including convection and radiation. Varying the amount of blood flow through the skin capillaries helps in controlling heat loss from the skin. When heat needs to be conserved, the sympathetic stimulation leads to vasoconstriction that reduces heat transfer from the body to the skin. Evaporation of sweat is an important method of heat loss.
- The ultimate control of body temperature is done by hypothalamic centres that control the heat loss and heat production. A rise in central temperature initiates mechanisms for loss of heat while a fall in temperature activates heat production and heat conservation.
- This helps in maintaining normal body temperature between 97 and 99°F (36.1 and 37.2°C).

Q.   Discuss various heat-related illnesses.

- High environmental temperatures may result in heat syndromes that include heat cramps, heat oedema, heat exhaustion, exertional heat injury and heat stroke.
- These syndromes occur primarily at high environmental temperatures (>32°C or 90°F) and at high relative humidity.

Predisposing Factors for Heat-Related Illnesses

Environment factors	Age
• High temperature	• Infants
• High relative humidity	• Elderly patients
Drugs/toxins	**Occupation**
• Anticholinergic agents	• Athletes
• Phenothiazines	• Labourers
• Cyclic antidepressants	• Military personnel
• Monoamine oxidase inhibitors (MAOI)	**Miscellaneous**
• Lysergic acid diethylamine (LSD)	• Use of alcohol
• Amphetamine	• Mental illnesses
• Lithium intoxication	• Heavy clothing
• Diuretics	• Hyperthyroidism
• Cocaine	
• Antihistamines	
• β-blockers	

Heat Cramps

- Most benign heat disorder, generally associated with strenuous physical activity.
- Pathogenesis: Direct exposure to sun is not required.
    - Loss of sodium in the sweat coupled with inadequate sodium replacement results in hyponatraemia that is thought to produce cramps through interference with calcium-dependent muscle relaxation.
    - Hyperventilation producing respiratory alkalosis and mild hypokalaemia may be a contributory factor.
- *Clinical features:*
    - Patients complain of painful spasm of skeletal muscles, both of extremities and abdomen.
    - Usually the cramps occur in the muscles that have been subjected to excessive exercise. The body temperature does not rise and the sweating is normal or excessive.
- Laboratory studies:
    - Mild hyponatraemia, hypokalaemia and respiratory alkalosis.
- *Treatment:*
    - Rest in a cool environment.
    - Replacement of sodium, potassium and water.
    - Avoid massage of the involved limbs as it generates heat.
- Prevention:
    - Liberal ingestion of sodium and water.

Heat Oedema

- It manifests by ankle and wrist swelling occurring in the first few days of heat exposure. It may be pitting in a few patients.
- The oedema resolves within a few days of acclimatisation.

Heat Exhaustion

- Heat exhaustion is common in elderly patients and occurs due to fluid and electrolyte losses coupled with inadequate replacement.
- *Clinical features:*
  - It is characterised by weakness, anxiety, fatigue, vertigo, thirst, anorexia, nausea, vomiting, headache, faintness, hyperventilation, muscular incoordination, agitation and confusion.
  - The skin is cold and clammy, the pupils are dilated, the pulse rate is rapid, the blood pressure is low and the body temperature is normal or mildly elevated.
  - The boundary between heat exhaustion and heat stroke is ill-defined; usually, the absence of signs and symptoms of severe CNS damage and core temperature below 39°C differentiate between the two.
  - Hepatic transaminases are normal in heat exhaustion.
- *Treatment:*
  - The patient should be moved to a cool area and given salt and water.
  - If severe volume depletion is present, intravenous fluids are given.
  - If temperature is markedly elevated, treatment of heat stroke should be instituted.

Exertional Heat Injury

- It occurs in persons who exert in hot and humid environment. It is common in long-distance runners who run without adequate hydration and acclimatisation.
- Clinical features:
  - This disorder is characterised by headache, piloerection, chills, hyperventilation, nausea, vomiting, muscular inco-ordination and incoherent speech.
  - The patients sweat freely and the body temperature is elevated but usually not as high as that seen with heat stroke.
  - Some patients may develop loss of consciousness.
  - Examination shows a diaphoretic patient with tachycardia and hypotension.
- Laboratory features:
  - Hypernatraemia, abnormal liver and muscle enzymes, hypocalcaemia, hypophosphataemia and hypoglycaemia.
  - Some patients also develop thrombocytopenia, disseminated intravascular coagulation and rhabdomyolysis.
- Treatment:
  - The patient should be placed in a cool place covered with wet cold sheets so as to lower the temperature below 100.4°F (38°C).
  - Massage of extremities is helpful in increasing flow of blood from the core to the periphery.
  - Infuse 5% dextrose in N/2 saline.

Heat Stroke

- Heat stroke is a true medical emergency that is characterised by hyperthermia and neurological symptoms.
- Heat stroke is of two types: exertional (increased endogenous heat production) and classic (impairment of heat dissipation).
- Exertional heat stroke:
  - It occurs in healthy, young individuals, usually during the period of acclimatisation who exert in hot environment. Typical patients are athletes and military recruits.
  - The patient develops hyperthermia and loss of consciousness.
  - The patient sweats freely.
  - Complications include DIC, rhabdomyolysis, renal failure and lactic acidosis.
- Classic heat stroke:
  - It occurs more often in elderly persons with underlying predisposing conditions during hot weather. These conditions impair thermoregulation, prevent removal from a hot environment, or interfere with access to hydration or attempts at cooling. Common examples include cardiovascular diseases, neurologic or psychiatric disorders, obesity, physical disability, extremes of age, use of alcohol or cocaine and use of drugs such as anticholinergic agents or diuretics.
  - Some persons develop unconsciousness without any premonitory features.

- Others may have headache, hyperventilation, vertigo, faintness, confusion and abdominal distress before losing consciousness.
  - Examination shows hyperthermia with a temperature more than 106°F (41.1°C) and in some cases may be as high as 112°F (44.3°C).
  - Most of the patients do not sweat and the skin is dry.
  - Other features include tachycardia, cardiac arrhythmias, low blood pressure, rapid respiration, flaccid muscles, decreased deep tendon reflexes, and lethargy, stupor or coma depending upon the severity.
  - The pupils may be fixed and dilated.
  - Complications in the form of lactic acidosis, DIC, rhabdomyolysis and renal failure are uncommon as compared to exertional heat stroke.
- Laboratory investigations show leucocytosis, proteinuria, elevated blood urea, respiratory alkalosis followed by metabolic acidosis (lactic acidosis), normo- or hypo-kalaemia, hypocalcaemia, hypophosphataemia, ST–T wave changes in the ECG, thrombocytopenia, coagulopathy and DIC.

Treatment

- Maintenance of airway, breathing and circulation.
- Measurement of rectal temperature.
- IV line and oxygen administration.
- Blood for various investigations.
- The patient should be totally disrobed.
- Application of ice on lateral aspects of the trunk, axillae and groins.
- Trunk and neck should be massaged so as to reduce vasoconstriction.
- Evaporative cooling involves the removal of clothing, spraying tepid water over the patient, and facilitating evaporation and convection with the use of a fan.
- Cold fluids intravenously.
- Immersing the patient in ice-cold water is equally or possibly more effective but is more cumbersome than the methods described above.
- Additional methods of lowering the body temperature that have been tried with varying success include ice water gastric lavage and enemas and ice water peritoneal dialysis.
- The goal is to reduce the core temperature to 100–102°F (37.8–38.9°C) within 1 hour.

Prevention

- Exertion should be limited when temperature and humidity are high.
- Activities in direct sunlight should be avoided.
- Loose clothes should be worn during summers.
- Adequate hydration should be maintained before and during exertion.

Q. What are the various causes of altered level of consciousness and hyperthermia?

Intrinsic causes	Extrinsic causes
• Central nervous system injury • Hyperthyroid storm • Infection (including cerebral malaria, meningitis) • Neuroleptic malignant syndrome • Phaeochromocytoma	• Anticholinergic poisoning • Drug ingestion (e.g. MAO inhibitors, amphetamines, phencyclidine) • Heat stroke

Q. Discuss briefly various causes of hyperthermia.

Causes	
• Anticholinergic syndrome • High fever due to infections • Heat stroke • Malignant hyperthermia	• Neuroleptic malignant syndrome • Drug interactions with MAO inhibitors • Serotonin syndrome

Malignant Hyperthermia

- Malignant hyperthermia is characterised by a rapid increase in temperature in response to inhalational anaesthetics (like halothane, cyclopropane, ether) or muscle relaxants (like succinylcholine).
- These are inherited disorders with inheritance varying from autosomal dominant to autosomal recessive mode.

Clinical Features

- Reduced muscle relaxation occurs during induction of anaesthesia and fasciculations occur when succinylcholine is administered. Some patients develop trismus during intubation.
- If the patient is not monitored carefully, sudden rise in temperature occurs resulting in a hot and dry skin.
- Other features include cardiac arrhythmia, muscle rigidity, hypotension and cyanosis.
- Complications include massive swelling of skeletal muscles, pulmonary oedema, DIC and acute renal failure.

King Syndrome

- It is the autosomal recessive form of malignant hyperthermia. It is associated with a number of congenital malformations including short stature, undescended testes, thoracic kyphosis, webbed neck, winged scapulae, low-set ears and antimongoloid obliquity of palpebral fissures of eyes.

Laboratory Features

- Respiratory and metabolic acidosis, hyperkalaemia and hypermagnesaemia.

Treatment

- Whenever malignant hyperthermia is suspected, surgery should be stopped and inhalational anaesthetic is withdrawn.
- Oxygen is administered and external cooling is started.
- Urine output is maintained by infusing fluids.
- Cardiac rhythm should be monitored for any arrhythmias.
- Specific treatment includes intravenous dantrolene in a dose of 1 mg/kg that is continued until improvement occurs or a dose of 10 mg/kg is reached.

Neuroleptic Malignant Syndrome (NMS)

- It is usually associated with therapeutic use of neuroleptic drugs like phenothiazines, butyrophenones and thioxanthines.
- The onset of NMS is not related to the duration of exposure to the agent or to the dose.

Clinical Features

- NMS typically develops over a period of 24–72 hours and lasts for 5–10 days.
- The typical features are hyperthermia, hypertonia of muscles, fluctuating levels of consciousness and instability of autonomic nervous system.
- Autonomic features include pallor, sweating, fluctuating blood pressure, tachycardia, urinary incontinence and cardiac arrhythmias.
- Death usually occurs between 3 and 30 days and is due to respiratory failure, cardiovascular collapse, renal failure and cardiac arrhythmias.

Laboratory Features

- Leucocytosis with shift to the left is common (less common in serotonin syndrome).
- Elevated liver enzymes and creatine kinase (less frequent in serotonin syndrome).
- Myoglobinuria and acute renal failure.
- Low serum iron.

Treatment

- Management focusses on withdrawal of the neuroleptic agent and meticulous supportive care that includes aggressive hydration and reduction of body temperature.
- Dantrolene and bromocriptine (2.5–10 mg T–D) have produced variable results.

Anticholinergic Syndrome

- It occurs in overdose with various agents (including neuroleptics) having anticholinergic properties.
- It is usually associated with peripheral features of anticholinergic poisoning that includes dry, flushed skin, dry mouth, dilated pupils, reduced bowel sounds and urinary retention.

- The patients are often hyperthermic and are disoriented and confused.
- Details under "datura poisoning".

Serotonin Syndrome

- Serotonin syndrome occurs due to an excess of serotonin in the CNS. The syndrome typically occurs with the co-administration of two serotonergic agents especially if the dose of one is escalated. It can also occur with monotherapy in susceptible patients and with overdose. The drug combination most commonly associated with severe reactions is that of MAOI and selective serotonin reuptake inhibitors (SSRI).

Clinical Features

- Onset of serotonin syndrome is rapid with CNS, neuromuscular and autonomic features.
- Change in mental status—agitation, delirium, restlessness, disorientation, anxiety, lethargy, seizures and hallucinations.
- Autonomic dysfunction—diaphoresis, hypertension, hyperthermia, vomiting, tachycardia, dilated pupils, unreactive pupils, diarrhoea and abdominal pain.
- Neuromuscular excitability—myoclonus, tremor, muscle rigidity, hyperreflexia and nystagmus.
- Others—rhabdomyolysis, acute renal failure, disseminated intravascular coagulation and circulatory failure.
- Unlike NMS, serotonin syndrome has rapid onset and is associated with hyperkinesia. Myoclonus is more common in serotonin syndrome as compared to NMS.

Treatment

- Stop all serotonergic drugs.
- Supportive care including supplemental oxygen, intravenous fluids and cardiac monitoring.
- Benzodiazepines for agitation.
- Esmolol for autonomic instability.
- Control of hyperthermia.

Q. Define hypothermia. Discuss clinical features and management of a patient with hypothermia.

- Hypothermia is defined as a core temperature less than 35°C (95°F):
  - Mild hypothermia — Core temperature 32° to 35°C (90° to 95°F).
  - Moderate hypothermia — Core temperature 28° to 32°C (82° to 90°F).
  - Severe hypothermia — Core temperature less than 28°C (82°F).
- Hypothermia is further classified into primary and secondary.
  - Primary or accidental hypothermia is usually acute and occurs in healthy individuals after acute exposure to low temperatures.
  - Secondary hypothermia is usually slow in onset and occurs in people with underlying predisposing illnesses.

Predisposing Factors

Individual factors	Drug/Toxin overdose
• Old age	• Phenothiazines
• Infants and young children	• Antidepressants
• Chronic alcoholics	• Barbiturates
• Immobilisation for a long time	• Alcohol
• Anorexia nervosa	
• Malnutrition	**Endocrine causes**
	• Hypopituitarism
Exposure to cold (accidental or environmental)	• Hypothyroidism
	• Hypoadrenalism
Central nervous system disorders	• Hypoglycaemia
• Stroke	
• Head Injury	**Miscellaneous**
• Tumour	• Septicaemia
• Wernicke's encephalopathy	• Massive transfusion with cold blood
	• Shock due to any cause
	• Burns

Clinical Features

- Patients with mild hypothermia develop tachypnoea, tachycardia, ataxia, dysarthria, impaired judgment, shivering and diuresis.
- In moderate hypothermia, patient develops bradycardia, hypoventilation, CNS depression, hyporeflexia and loss of shivering. Paradoxical undressing may be observed. Atrial fibrillation and other arrhythmias may occur and the electrocardiogram may contain Osborn J waves.
- Severe hypothermia can lead to pulmonary oedema, oliguria, coma, hypotension, severe bradycardia, ventricular tachycardia and fibrillation and asystole.

Diagnosis

- A low-reading thermometer is required to determine core temperature (generally rectal or oesophageal temperature is taken).
- Arterial blood gas analysis may show metabolic and respiratory acidosis.
- Coagulopathy.

Treatment

- Stabilisation of airway, breathing and circulation.
- Avoid rough movements of the patient as hypothermic heart is very sensitive to movement and rough handling may precipitate arrhythmias, including ventricular fibrillation.
- Cardiac arrest due to ventricular arrhythmias and asystole may be refractory to conventional CPR until the patient has been rewarmed. Hypothermic patients in cardiac arrest should receive defibrillation and pharmacologic therapy as indicated. CPR should not be abandoned unless the patient has been rewarmed to 34-35°C
- Rewarming:
  - Passive external rewarming is the method of choice for mild hypothermia. After wet clothing is removed, the patient is covered with blankets. The resulting reduction in heat loss combines with the patient's intrinsic heat production to produce rewarming.
  - Active external rewarming includes application of warm blankets, heating pads, heat from radiant heaters or forced warm air either singly or in combination. These methods are indicated for moderate to severe hypothermia.
    - A risk of active external rewarming is core temperature after drop. This complication occurs when the extremities and trunk are warmed simultaneously. Cold, acidotic blood which has pooled in the vasoconstricted extremities of the hypothermic patient returns to the core circulation, causing a drop in temperature and pH. This phenomenon may explain fatal dysrhythmias which sometimes occur during rewarming. Core temperature after drop can be avoided by rewarming the trunk before the extremities.
  - Active internal rewarming can be combined with active external rewarming in moderate to severe hypothermia. Various techniques include warm humidified oxygen, warm intravenous fluids, bladder or gastric irrigation with warm saline, pleural and peritoneal irrigation with warm saline, continuous arteriovenous or venovenous rewarming, haemodialysis and cardiopulmonary bypass.

Chapter 11

Nutritional Factors in Disease

Q. Give a brief account of calcium, vitamin D, parathyroid hormone and calcitonin.

Calcium

- Calcium salts (hydroxyapatite) are present in the cellular matrix that provides the hard structure of the bones and teeth—99% of total body calcium is thus present in the skeleton. The human body of an adult contains about 1200 g of calcium. Calcium absorption from the intestines is dependent on vitamin D and parathyroid hormone (PTH).

Dietary sources of calcium	Recommended intake
• Milk and milk products (cheese, yoghurt) • Shell fish and fish eaten with bone	• Children—500–600 mg/day • Adolescents—700–800 mg/day • Post-menopausal females—1000 mg/day • Pregnancy and lactation—1200 mg/day

Vitamin D

- Vitamin D is a fat-soluble vitamin having the basic biochemical structure as that of cholesterol. Two chemical forms are present.

Ergocalciferol (vitamin D₂)

- This is manufactured by the action of ultraviolet light on ergosterol present in fungi. It is not present in humans. It is often used for therapeutic purposes.

Cholecalciferol (vitamin D₃)

- Naturally occurring form of vitamin D; also known as vitamin D_3.
- Formed in the skin by the action of ultraviolet light on 7-dehydrocholesterol.
- Cholecalciferol is converted in the liver to 25-hydroxycholecalciferol (25-OH-D_3), which is further hydroxylated in the kidney to active vitamin D, 1-α,25-dihydroxycholecalciferol [1,25(OH)$_2$D$_3$] or calcitriol. This enzyme required for conversion is present mainly in proximal tubules of kidneys; it has also been described in immune cells (macrophages and dendritic cells), bone, epithelia and parathyroid gland.

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        ┌─────────────────────┐
        │ 7-Dehydrocholesterol│
        └─────────────────────┘
                  │          ┌──────────────────┐
                  │ ◄────────│ Skin             │
                  ▼          │ Ultraviolet light│
        ┌──────────────────────────┐ └──────────┘
        │ Cholecalciferol (vitamin D₃)│
        └──────────────────────────┘
                  │          ┌──────────────────────┐
                  │ ◄────────│ Liver                │
                  ▼          │ Vitamin D₃-25 hydroxylase│
        ┌──────────────────┐ └──────────────────────┘
        │ Calcidiol (25[OH]D₃)│
        └──────────────────┘
                  │          ┌───────────────────────────┐
                  │ ◄────────│ Kidney                    │
                  ▼          │ 25(OH)D₃-1-α-hydroxylase  │
        ┌──────────────────────────┐ └─────────────────┘
        │ Calcitriol (1,25[OH]₂D₃) │
        └──────────────────────────┘
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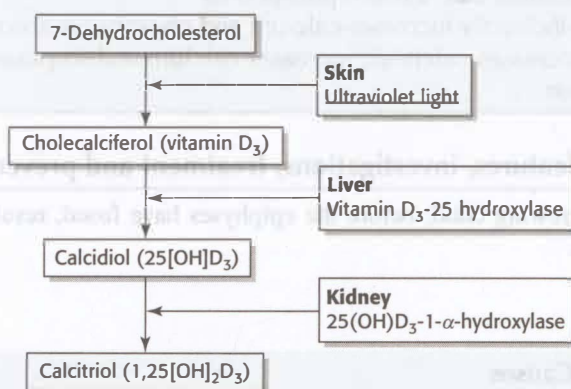
- The function of active vitamin D includes induction of a specific transport protein in the enterocyte to increase calcium absorption. It also increases phosphate absorption though the gut.
- Dietary sources of vitamin D are fish and cod liver oil, eggs, liver and fatty fish.

Effects of calcitriol

- **Intestines**
  - Increased calcium absorption
  - Increased phosphorus absorption
  - Decreased magnesium absorption
- **Parathyroid glands**
  - Decreased PTH synthesis
  - Decreased PTH secretion
- **Bone**
  - Increased mineralisation indirectly via increased calcium absorption in intestinal lumen
  - At high doses: increased osteoclastic bone
- **Kidney**
  - Autoregulation of calcitriol production by the kidney

Parathyroid Hormone

- PTH is secreted by parathyroid glands in response to low serum calcium levels. It raises calcium levels by:
  - Accelerating osteoclastic bone resorption.
  - Increasing renal tubular reabsorption of calcium.
  - Increasing 1,25-dihydroxycholecalciferol, which raises serum calcium.
- The increase in calcium in response to the effects mediated by PTH acts via a classic endocrine feedback loop on the calcium-sensing receptors on parathyroid glands, thereby decreasing secretion of PTH.
- PTH causes phosphate loss through kidneys producing hypophosphataemia.

Calcitonin

- It is secreted by the parafollicular C cells of thyroid.
- It is a weak inhibitor of osteoclast activation and opposes the effects of PTH on the kidneys, thereby promoting calcium and phosphate excretion.

Functions of Chemicals Involved in Bone Formation

Chemical	Function
• Calcitonin	Bone—inhibits resorption Intestine—inhibits calcium and phosphorus absorption Kidney—increases calcium excretion, inhibits production of calcitriol
• Calcitriol	Bone—indirectly stimulates bone synthesis via increased calcium absorption in intestinal lumen. Intestine—increases calcium and phosphorus absorption Kidney—autoregulation of calcitriol production by the kidney Parathyroid gland—negative feedback to decrease secretion of PTH
• PTH	Bone—mobilises calcium and phosphorus Intestine—indirectly increases calcium and phosphorus absorption by increasing calcitriol Kidney—increases calcitriol, increases calcium reabsorption, decreases phosphorus reabsorption

Q. Write briefly on clinical features, investigations, treatment and prevention of rickets.

- Deficiency of vitamin D in a growing child, before the epiphyses have fused, results in failure of growing bone to mineralise. This leads to rickets.

Causes and Types

Types of rickets	Causes
• Secondary rickets	Due to malabsorption states, e.g. coeliac disease, intestinal resection; inadequate intake of calcium, vitamin D; inadequate sunlight exposure
• Resistant rickets	These cases are resistant to ordinary therapeutic doses of vitamin D, e.g. familial hypophosphataemic rickets and vitamin D-dependent rickets (type I/II)
• Renal rickets	Seen in cases of chronic renal failure

Types of rickets	Causes
• Drug-induced rickets	Antivitamin D effect, e.g. anticonvulsants like phenytoin sodium
• Tumour-induced rickets	Due to underlying malignancy

- Dark-skinned persons require more sunlight exposure than others to produce the same amount of vitamin D because melanin acts as a neutral filter and absorbs solar radiation.
- Vitamin D-dependent rickets, type I (also known as pseudovitamin D deficiency rickets) is secondary to a defect in the gene that codes for the production of renal $25(OH)D_3$-1-α-hydroxylase. It is an autosomal recessive disorder.
- Vitamin D-dependent rickets, type II (or hereditary vitamin D resistant rickets) is a rare autosomal disorder caused by mutations in the vitamin D receptor. It results in failure of vitamin D dependent calcium absorption that in turn produces hypocalcaemia and rickets. This form of rickets does not respond to vitamin D treatment. Elevated levels of circulating calcitriol differentiates this type from type I.
- Familial hypophosphataemic rickets also produce vitamin D-resistant rickets refractory to vitamin D treatment. Renal wasting of phosphorus at the proximal tubule level results in hypophosphataemia. Normal levels of calcitriol are found in this disorder.
- In rickets secondary to malignancy, the most common pathophysiology is tumour secretion of a renal phosphate wasting factor and impaired calcitriol production.

Clinical Features

- Commonly, infants younger than 6 months present with hypocalcaemic tetany or seizures, whereas older children present with failure to thrive or skeletal deformities.
- Infant appears well nourished but is restless, fretful and pale with flabby muscles.
- Prone to respiratory and gastrointestinal infections.
- Retardation of skeletal growth leads to failure to sit, stand, crawl and walk at the normal ages.
- Poor dentition and late eruption.
- Craniotabes with "egg shell crackling" feeling (soft skull bones). The skull has small round unossified areas in the membranous part.
- Enlargement of the epiphyses at the lower end of radius, femur, tibia and fibula.
- "Rickety rosary" (enlargement of costochondral junctions visible as beading along the anterolateral aspects of the chest) and pigeon-shaped chest (pectus carinatum).
- Harrison's groove or sulcus at the lower margin of the thorax caused by muscular pull of diaphragmatic attachments to the lower ribs.
- Frontal bossing of skull.
- Delayed closure of anterior fontanelle.
- Kyphosis, genu valgum or genu varum (knock knees or bow legs).
- Pelvic abnormalities—triradiate pelvis.
- Infantile tetany—due to low serum ionised calcium, resulting in epileptic fits and vocal cord spasm (high-pitched distressing cry).

Investigations

- Wrist radiography—lower ends of the shaft of radius and ulna become splayed, and epiphyseal surfaces appear fuzzy and ill-defined. Unossified zone between shaft and radial epiphysis is widened ("saucer" deformity).
- Low serum calcium.
- Low serum phosphate (due to associated secondary hyperparathyroidism).
- Increased alkaline phosphatase activity (due to increased osteoblast activity).
- Plasma 25-hydroxyvitamin D_3 levels are low in most cases.

Treatment

- Correction of an underlying cause.
- Supplementation of dietary sources of calcium and vitamin D.
- For nutritional deficiency of vitamin D, ergocalciferol, 150,000–600,000 IU orally or intramuscularly as a single dose. Another option is to give ergocalciferol in a dose of 2000 IU everyday. Cholecalciferol can be given in place of ergocalciferol in a dose of 60,000 IU orally every week or 2000 IU every day.
- For type I vitamin D-dependent rickets, calcitriol is required.
- For type II vitamin D-dependent rickets, high doses of calcitriol and calcium may be tried.
- Familial hypophosphataemic rickets is treated with oral phosphorus and calcitriol.

Prevention

- Adequate intake of vitamin D (1000–5000 IU/day).
- Adequate sunlight exposure (from 30 minutes to 2 hours/week for infants).

Q. Describe hypervitaminosis D.

- Chronic ingestion of large doses of vitamin D (50–100 times the normal physiologic requirement, i.e. more than 50,000–100,000 IU/day) causes certain toxic symptoms and hypercalcaemia.

Symptoms

- Nausea, vomiting, and constipation.
- Polyuria and renal calculi.
- Drowsiness.
- Signs of renal failure.
- Metastatic calcification in arteries and kidneys due to hypercalcaemia.

Diagnosis

- Increased serum level of vitamin D.
- Hypercalcaemia.

Q. Discuss role of vitamin D in various diseases.

- Active form of vitamin D is 1, 25-dihydroxyvitamin D.
- Most tissues and cells in humans express vitamin D receptors (VDR).
- Vitamin D influences genes regulating many key cellular functions including cellular proliferation, differentiation, apoptosis and angiogenesis.
- Serum 25-OH-D_3 levels most accurately reflect vitamin D status. The cut-offs representing insufficient and deficient 25-OH-D_3 are variable, but most physicians take vitamin D deficiency as 25-OH-D_3 levels less than 20 ng/mL and vitamin D insufficiency as 25-OH-D_3 levels between 21 and 29 ng/mL. Deficiency of vitamin D may lead to several diseases. However, for many of them, robust evidence is not available.

Rickets

- Refer before.

Osteoporosis

- Strong link between vitamin D deficiency and osteoporosis especially in the elderly.
- Vitamin D deficiency is associated with marked suppression of intestinal calcium absorption and impairment of calcium balance, which results in low bone mineral content and density.

Muscle Weakness

- Muscle weakness is a prominent feature of vitamin D deficiency. This can lead to an increased number of falls.

Hypertension

- Growing evidence suggests that vitamin D has an important association with blood pressure.
- $1,25\text{-(OH)-D}_3$ may inhibit renin expression in the kidneys and blocks proliferation of vascular smooth muscle cells, which could influence blood pressure.

Coronary Artery Disease

- Many studies support association between low vitamin D levels and increased cardiovascular adverse events.
- Vitamin D deficiency is associated with impaired endothelial function and vascular stiffness, which are known predictors of long-term cardiovascular morbidity and mortality.
- Inflammation has been shown to have a strong role in the pathogenesis of CAD. Vitamin D suppresses inflammation via several pathways:
  - Inhibition of prostaglandin and cyclooxygenase-2 pathways.
  - Reduction of matrix metalloproteinase-9.
  - Up-regulation of anti-inflammatory cytokine interleukin-10.

Cancer

- Vitamin D is one of the most potent hormones for regulating cell growth.
- It can induce differentiation into normally functioning cells, and inhibit proliferation, invasiveness, angiogenesis, and metastatic potential.
- The protective relationship between sufficient vitamin D status and lower risk of cancer has been found in many studies, particularly with regard to colorectal cancer.

Diabetes

- Vitamin D deficiency inhibits pancreatic secretion and turnover of insulin. This may result in impaired glucose tolerance and frank diabetes.
- Vitamin D increases insulin sensitivity.

Tuberculosis

- Studies have shown that patients with TB have lower 25-(OH)-D$_3$ levels in comparison with those without TB.

Other Associations with Reduced Vitamin D

- Increased severity of infectious diseases.
- Reduced immunity.
- Increased frequency of mood disorders.
- Increased frequency of inflammatory bowel disease.
- Increased autoimmunity.

Q. What is renal bone disease? Explain.

Q. Describe renal osteodystrophy.

- In chronic renal failure, the diseased kidney fails to synthesise 1,25-dihydroxyvitamin D$_3$. This results in impairment of calcium absorption from the gut. As the GFR falls, the serum phosphate concentration begins to rise. This phosphate retention in plasma facilitates calcium entry into the bone, thereby contributing to hypocalcaemia. This triggers PTH release resulting in secondary hyperparathyroidism.
- Renal or metabolic osteodystrophy is caused by:
  - Disordered vitamin D metabolism (reduced formation of 1,25-dihydroxyvitamin D$_3$).
  - Renal phosphate retention.
  - Secondary hyperparathyroidism.
  - Chronic metabolic acidosis of renal failure.
  - Excessive faecal loss of calcium.
  - Aluminium toxicity due to absorption of aluminium from antacids used as phosphate binders.
- Even with high serum PTH level, there is a skeletal resistance to its actions; thus serum calcium level remains low.

Types of Renal Osteodystrophy

- Renal osteodystrophy can be divided according to the rate of bone turnover:
  - High bone turnover osteodystrophy seen due to secondary hyperparathyroidism and include osteitis fibrosa cystica and osteosclerosis.
  - Low bone turnover osteodystrophy occurs with low PTH level. There is impaired mineralisation activity with decreased number of osteoblasts and osteoclasts. Various entities include rickets or osteomalacia, aluminium-related bone disease and adynamic bone disease (ABD). ABD occurs due to excessive suppression of PTH by use of calcium-based phosphate binders, vitamin D, and following parathyroidectomy. Mortality is increased because of enhanced cardiovascular calcification.
  - Mixed type osteodystrophy is osteitis fibrosa and osteomalacia with impaired mineralisation. The serum PTH level is high.
- In children—impaired bone growth results in renal rickets or renal dwarf.
- In adults—osteomalacia.

Clinical Features

- Most patients with renal osteodystrophy are asymptomatic.
- Some patients present with symptoms of an acute arthritis (pain, swelling, erythema, warmth and decreased range of motion).
- Bone pain is rare, and is seen usually with osteomalacia.

- Skeletal deformities (e.g. genu valgum), more common in uraemic children.
- Pathological fractures can occur in some cases.
- These patients may have calciphylaxis that includes both soft tissue and vascular calcifications, including coronary artery calcification. This occurs when calcium × phosphate >70 mg/dL.

Radiographic Findings

- The classic radiographic finding of secondary hyperparathyroidism is subperiosteal bone resorption and erosions. The earliest findings usually occur on the radial aspect of the middle phalanges, but can progress to include proximal tibia, distal clavicle, radius and ulna and humeral and femoral necks. These lesions are due to osteitis fibrosa cystica.
- Brown tumours may be seen on plain film as radiolucent, cystic regions, often within cortical bone. These lesions are again due to osteitis fibrosa cystica.
- Osteosclerosis is typically seen in the vertebrae, with a striped appearance on lateral spine films demonstrating alternating areas of radiopacity and radiolucency ("rugger jersey spine").
- Osteopenia.
- Findings of osteomalacia in adults.

Treatment

- The current approach seeks to maintain calcium and phosphate in the normal range.
- Lowering phosphate is done initially by dietary restriction of phosphate intake to 800 to 1000 mg/day
- Agents commonly used in the management of renal osteodystrophy include calcium tablets, vitamin D supplements (in the form of calcitriol) and phosphate binders such as calcium carbonate or calcium acetate.
- Newer vitamin D analogues like paricalcitol, which has minimal effects on gut absorption of calcium. It is an active analogue based on vitamin D_2 structure (19-nor-1,25-dihydroxyvitamin D_2) that suppresses PTH secretion, but has minimal effect on serum level of calcium and phosphate.
- Use of calcium-containing phosphate binders may lead to calcium overload. Newer calcium free phosphate binders include sevelamer hydrochloride, lanthanum carbonate, magnesium citrate and ferric citrate.
- Calcimimetics (e.g. cinacalcet) decrease secretion of serum PTH through stimulation of calcium-sensing receptors in the parathyroid gland, which reduces renal osteodystrophy.

Q. Discuss the causes, clinical features, investigations and treatment in case of osteomalacia.

- It is a disorder of mineralisation of the organic matrix of the skeleton in adults, when the epiphyseal growth plates have closed. This produces increased unmineralised matrix. In contrast, in rickets, the growing skeleton is involved.

Aetiology

- A number of disorders can produce osteomalacia, primarily through alteration in vitamin D nutrition or metabolism or because of phosphate wasting.

Nutritional abnormalities • Dietary deficiency of vitamin D • Parenteral nutrition	**Acidosis** • Distal renal tubular acidosis (type I) • Ureterosigmoidostomy
Malabsorption • Tropical sprue • Coeliac disease • Hepatobiliary diseases • Pancreatic insufficiency	**Phosphate depletion** • Use of non-absorbable antacids • X-linked hypophosphataemia • Tumour-associated osteomalacia
Disorders of vitamin D metabolism • Vitamin D dependency type I and type II • Use of anticonvulsants • Chronic renal failure	**Miscellaneous** • Multiple myeloma • Nephrotic syndrome • Lead poisoning • Inadequate sun exposure • Obesity

Clinical Features

- Bone pains and muscle weakness.
- Pain in the hip may produce antalgic gait.
- Proximal muscle weakness produces waddling gait and may mimic a primary muscle disease.
- Fractures of bones with mild trauma.
- Collapse of vertebrae produces local pain and deformity.
- Deformities due to softening of skeleton and include kyphosis, coxa vera, pigeon chest and triradiate pelvis with a narrow pubic arch.

Investigations

- Low or normal serum calcium (secondary hyperparathyroidism causes release of calcium from bone and increased resorption of calcium by the kidney; this maintains normal serum calcium in most patients).
- Low serum phosphorus.
- Elevated serum alkaline phosphatase.
- Reduced urinary excretion of calcium.
- Low serum 25-hydroxyvitamin D_3 levels (<20 ng/mL).
- Elevated PTH levels.
- Radiological features:
  - Reduced bone density (osteopenia).
  - Epiphyseal growth plate is increased in thickness, cupped and hazy at the metaphyseal border.
  - Presence of nontraumatic fractures.
  - Radiolucent, 2–5 mm wide bands called pseudofractures (Looser's zones) are seen. Often bilateral and symmetric and lie perpendicular to the cortical margins of bones. Usually found at femoral neck, on the medial part of the femoral shaft, and in the pubic and ischial rami.
  - Cortical thinning due to secondary hyperparathyroidism.
  - Loss of radiologic distinctness of vertebral body trabeculae followed by concavity of the vertebral bodies (codfish vertebrae).
- Bone scan may be normal or may show discrete foci of increased radionuclide uptake.
- Bone mineral density, as assessed by dual-energy X-ray absorptiometry (DEXA) is reduced at spine, hip and forearm, with the greatest deficits at the cortical-rich bone in the forearms.

Treatment

- Dietary deficiency is corrected by 1000–4000 IU of vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol) for 3 months followed by lower doses as maintenance.
- Patients with osteomalacia due to malabsorption require 50,000–100,000 IU of vitamin D along with calcium supplementation. Small doses of calcitriol (0.5–1.0 μg daily) are also effective.
- In chronic renal failure, calcitriol is required with weekly monitoring of serum calcium.

Q. Discuss briefly clinical features, investigations and treatment of osteoporosis.

- Osteoporosis is characterised by a reduction in the mass of bone per unit volume (osteopenia) to a level below that required for adequate mechanical support function. There is no abnormality in the ratio of the mineral to organic phase of bone matrix.
- Osteoporosis is also defined operationally as a bone density that falls 2.5 standard deviation below the mean for a 30-year-old normal reference in that population (also known as *T* score of 2.5).

Common Disorders Associated with Osteoporosis

Nutritional and GI disorders	Inherited disorders
- Malnutrition	- Osteogenesis imperfecta
- Malabsorption syndromes	- Marfan syndrome
- Severe liver disease	- Haemochromatosis
	- Porphyria

Endocrine disorders
- Cushing's syndrome
- Thyrotoxicosis
- Hyperparathyroidism
- Acromegaly
- Hypogonadism

Rheumatological disorders
- Rheumatoid arthritis
- Ankylosing spondylitis

Drugs
- Chronic steroid therapy
- Chronic phenytoin therapy
- Chronic heparin therapy
- Antiretroviral drugs
- Calcineurin inhibitors (tacrolimus, cyclosporine)
- Aromatase inhibitors (anastrozole, letrozole)

Miscellaneous
- Immobilisation
- Postmenopausal
- Pregnancy and lactation
- "Senile" osteoporosis

Clinical Features

- Fracture is the only cause of symptoms in osteoporosis that produces sudden pain. Common sites of fractures include spine, hip and wrist joints. Vertebral fractures can occur without any pain also.
- Vertebral and wrist fractures can occur much before hip fractures.

Laboratory Investigations

- These include serum calcium, alkaline phosphatase, urinary calcium and other relevant investigations for the suspected underlying cause. Most often, serum calcium and alkaline phosphatase are normal.
- Urinary levels of cross-linked N-telopeptides of type I collagen (NTx) indicate the rate of bone breakdown or turnover. Urine NTx >40 nmol/L indicate excessive bone turnover, and is a feature of osteoporosis.
- Radiographs of spine and pelvis:
  - Reduced cortical thickness of bones.
  - Increased radiolucency of bones.
  - Vertebrae show "codfish" appearance.
  - Collapse of vertebral body with kyphosis.
- Measurement of bone density:
  - CT scan.
  - Ultrasound.
  - DEXA scan.

Treatment

- Diet should include at least 1 g of calcium and 800–1000 IU of vitamin D daily. Additional supplementation may be done, if required to maintain bone and muscle strength.
- Ensure adequate weightbearing exercises.
- Smoking and alcohol should be stopped.
- Reduce falls by taking care of home safety and personal precautions.
- If steroids are required for chronic use, add calcium, vitamin D and bisphosphonates.

Bisphosphonates

- Most effective agents for reducing osteoporotic fractures.
- Typically combined with calcium and vitamin D.
- Bisphosphonates suppress osteoclast mediated bone resorption. They also accelerate osteoclast apoptosis.
- Include alendronate, risedronate, ibandronate and zoledronic acid or zoledronate.
- Indicated for treatment of osteoporosis in postmenopausal females and corticosteroid-induced osteoporosis.
- Alendronate, risedronate and zoledronic acid reduce development of both hip and vertebral fractures while ibandronate does not reduce hip fractures.
- Alendronate also indicated in males with osteoporosis.
- Food reduces absorption of bisphosphonates; therefore, these agents should be taken at least 30 minutes before the first food. Tablets should be swallowed with 200–300 mL of water. To reduce the risk of gastroesophageal irritation, patients should remain upright for at least 30 minutes after dosing.

- Dose:
  - Risedronate: 5 mg orally once a day or 35 mg orally once a week.
  - Alendronate: 10 mg orally once a day or 70 mg orally once a week.
  - Ibandronate: 150 mg once a month.
  - Zoledronic acid: 5 mg intravenously once in a year.
- Main side effect is gastrointestinal upset. An important complication is osteonecrosis of jaw. Other adverse effects include bone, joint and/or muscle pains. Zoledronic acid may result in flu-like symptoms and fever.
- Also useful in Paget's disease and in painful bone metastasis (with or without hypercalcaemia). Intravenous pamidronate is useful in severe hypercalcaemia.

Hormone Replacement Therapy (HRT)

- Hormone replacement therapy (HRT) is effective for the prevention of postmenopausal osteoporosis.
- However, it is associated with increased risks of breast cancer, coronary artery disease, stroke and pulmonary thrombo-embolism. Hence, it is not recommended.

Recombinant Human Parathyroid Hormone

- PTH increases the rate of bone remodelling and results in a positive remodelling balance, leading to thicker osteons.
- Teriparatide, a recombinant human PTH, is approved for the treatment of postmenopausal osteoporosis for a period of maximum of 2 years.
- Dose is 20 μg subcutaneously once a day.

Selective Oestrogen Receptor Modulators

- Raloxifene is indicated for the prevention and treatment of postmenopausal osteoporosis.
- Dose is 60 mg orally once a day.
- Increased risk of thromboembolism.

Salmon Calcitonin

- Inhibits bone resorption by acting directly on osteoclasts.
- Indicated for treatment of osteoporosis if patient is intolerant to other agents.
- Available in both injectable and intranasal spray preparations.
- Dose is 200 IU intranasally once a day (alternating nostrils daily) or 100 units subcutaneously or intramuscularly every other day.

Strontium Ranelate

- Strontium ranelate is a dual action bone agent that has proven efficacy in the prevention of both vertebral and non-vertebral fractures in patients over the age of 80.
- It stimulates proliferation of osteoblasts and inhibits proliferation of osteoclasts.
- Therefore, it increases bone mineral density by forming new bone.
- Dose is 2 g orally daily and is used in patients where bisphosphonate treatment has failed or is contraindicated.

Denosumab

- A fully human monoclonal antibody to receptor activator of nuclear factor kappa-B ligand (RANKL), an osteoclast-differentiating factor.
- Inhibits osteoclast formation, thus decreasing bone resorption.

Q. Write a brief note on corticosteroid-induced osteoporosis.

- Oral corticosteroid therapy using more than 5 mg of prednisolone (or equivalent) daily for more than 3 months can lead to a reduction in bone mineral density and an increase in the risk of fractures.

Pathogenesis

- Suppression of osteoblast function resulting in decreased bone formation (primary effect).
- Suppression of intestinal calcium absorption.
- Reduced renal tubular calcium reabsorption with increased urinary calcium excretion.
- Renal and intestinal losses of calcium result in development of secondary hyperparathyroidism that produces increase in bone resorption and bone turnover.

- Increased sensitivity of bone cells to PTH.
- Apoptosis of osteoblasts and osteocytes.

Prevention and Treatment

- Bisphosphonates.
- Vitamin D.
  - Active forms of vitamin D (alfacalcidol, 1α-hydroxy-vitamin D_3 and calcitriol) and non-active forms (cholecalciferol and ergocalciferol) prevent bone mass loss in chronic corticosteroid users.
  - However, use of non-active forms may not reduce incidence of fractures
- Fluorides.
- Calcium carbonate (1,000 mg/day) in combination with vitamin D.
- Calcitonin.
- Oestrogens.
- Teriparatide (a recombinant PTH).

Q. Write a brief note on scurvy.

- This is caused by ascorbic acid deficiency (vitamin C) that results in defective formation of collagen in connective tissue. There is failure of hydroxylation of proline to hydroxyproline.

Types of Scurvy

- Adult scurvy.
- Infantile scurvy.

Adult Scurvy

- Swollen and spongy gums—"scurvy buds".
- Scorbutic gingiva—gingivitis, loosening of teeth and bleeding gums.
- Perifollicular hyperkeratotic papules.
- Perifollicular haemorrhages.
- Deformed "corkscrew" hair projects out of a follicle.
- Petechial haemorrhages, ecchymoses, epistaxis and gastrointestinal bleeding.
- Nail beds—splinter haemorrhages.
- Haemorrhage into muscles of arms and legs with secondary phlebothrombosis.
- Haemorrhages into joints.
- Poor wound healing.

Infantile Scurvy

- Subperiosteal haemorrhage into shafts of long bones.
- "Scorbutic rosary" denotes enlargement of costochondral junctions.
- Purpura or ecchymotic skin lesions.
- Gingival changes.
- Retrobulbar, subarachnoid and intracerebral haemorrhages.
- Lassitude.
- Anorexia.
- Painful limbs giving rise to "pseudoparalysis".

Management

- Consumption of citrus fruits and vegetables.
- Vitamin C 500 mg daily initially.

Q. Discuss beriberi/vitamin B_1 (thiamine) deficiency.

- Vitamin B_1 is essential for the coenzyme thiamine pyrophosphate. It is required:
  - for decarboxylation of pyruvate (glycolytic pathway) to acetyl CoA (Krebs cycle).
  - for transketolase in the hexose monophosphate (HMP/pentose) shunt pathway.
  - for decarboxylation of α-ketoglutarate to succinate (Krebs cycle).

- Thiamine deficiency, therefore, results in the following abnormalities:
  - Defective aerobic cellular glucose utilisation.
  - Pyruvic acid and lactic acid accumulation that produces vasodilatation and increased cardiac output.

Clinical Syndromes of Thiamine Deficiency

- Wet beriberi—a high cardiac output failure.
- Dry beriberi—a type of peripheral neuropathy.
- Wernicke's encephalopathy.
- Korsakoff's psychosis.

Wet Beriberi

- Oriental beriberi is caused by eating diets in which most of the calories are derived from polished, highly milled rice.
- Oedema—caused by the metabolites like pyruvate and lactate, which cause extreme peripheral vasodilatation and leakage of fluid through capillaries.
- Beriberi heart disease is characterised by the following features:
  - Peripheral vasodilatation.
  - High cardiac output state with warm extremities.
  - Biventricular failure.
  - Retention of sodium and water.
  - Extreme tachycardia.
  - Venous congestive state characterised by raised JVP and tender hepatomegaly.
  - Hyperdynamic circulation with a rapid circulation time.
  - Dyspnoea and cardiovascular collapse.
  - Marked cardiomegaly.

Biochemical Tests

- Measurement of blood thiamine, pyruvate and lactate levels.
- Whole blood or erythrocyte transketolase activity.

Management

- Complete bed rest.
- 100 mg thiamine IM for the first 7 days, then 10 mg/day orally for several months.

Dry Beriberi

- Nutritional polyneuropathy is characterised by symmetric impairment of sensory, motor and reflex functions that affect the distal segments of limbs more severely than the proximal ones.
- Histology—non-inflammatory degeneration of myelin sheaths (demyelination).
- There are three types of nervous system involvement in beriberi:
  - Peripheral neuropathy.
  - Cerebral beriberi, i.e. Wernicke's encephalopathy.
  - Korsakoff's syndrome.

Q. Describe Wernicke's encephalopathy.

- Wernicke's encephalopathy is an acute neuropsychiatric condition due to an initially reversible biochemical brain lesion caused by depletion of vitamin B_1 (thiamine).

Causes

- Chronic alcohol use
- Protein-calorie malnutrition from malabsorption or forced/self-imposed inadequate diet
- Patients with protracted vomiting
- Carbohydrate loading (intravenous or oral) when thiamine stores are minimal
- Chronic renal failure
- Hyperalimentation, AIDS, and drug misuse
- Genetic abnormality of transketolase enzyme

Clinical Features

- Mental disturbances:
    - Progressive depression of the state of consciousness.
    - Global confusional apathetic state, profound listlessness, inattentiveness and disorientation.
- Paralysis of eye movements:
    - VIth nerve palsy and diplopia.
    - Nystagmus.
    - Internuclear ophthalmoplegia.
- Ataxia of gait—this affects stance and gait predominantly.

Management

- Wernicke's disease represents a medical emergency, and its recognition demands immediate administration of thiamine. Dose is 100 mg intravenously or intramuscularly everyday for 7 days followed by oral thiamine. There is prompt reversibility within hours of administration of thiamine, especially the ocular signs and later the ataxia.
- Magnesium is often required as it is a cofactor required for normal functioning of thiamine-dependent enzymes.
- Intravenous glucose solutions should not be given particularly in malnourished patients, as they may exhaust the patient's reserve of B vitamins and either precipitates Wernicke's disease in a previously unaffected patient or cause a rapid worsening of an early form of the disease.

Q. What is Korsakoff's psychosis?

- This thiamine deficiency induced metabolic central nervous system disease predominantly affects memory. This is characterised by confabulation and defect in retentive memory (severe defect in storing new information and learning).
- It may follow Wernicke's encephalopathy or can develop on its own.
- Symptoms include:
    - Apathy, drowsiness and global confusion.
    - Confabulation.
    - Amnesic state characterised by large gaps in memory (both antegrade and retrograde memory loss).
- Korsakoff's psychosis is the psychic component of Wernicke's encephalopathy. When both the ocular ataxic and amnesic symptoms can be recognised the disease is designated as Wernicke–Korsakoff syndrome.
- Treatment includes parenteral thiamine (100 mg IM daily for 7 days). The outcome of Korsakoff's psychosis varies. Complete or almost complete recovery occurs in less than 20% of patients. The recovery is gradual and incomplete in the remainder of patients.

Q. Write briefly on the clinical features and management of niacin deficiency (pellagra).

- Pellagra (meaning 'raw' skin) is a metabolic encephalopathy caused by niacin (nicotinamide) deficiency.

Causes

- Inadequate intake—Malnutrition, maize diet, jowar (sorghum) diet, chronic alcoholism, anorexia nervosa
- Malabsorption—Refer before
- Drug-induced—6-mercaptopurine, 5-fluorouracil, azathioprine, carbamazepine, isoniazid, phenytoin and phenobarbitone

Clinical Features

1. Dermatitis. ⎫
2. Diarrhoea. ⎬ 3Ds
3. Dementia. ⎭
    - Early mental symptoms include:
        - Insomnia.
        - Fatigue.
        - Anxiety, nervousness and irritability.
        - Depressive symptoms.
        - Dementia features.

- Spinal cord affection:
  - Involvement of the posterior and lateral columns.
  - Spastic paretic syndrome characterised by spastic weakness of legs, with absent abdominal and increased tendon reflexes, clonus and extensor plantar responses.
- Skin manifestations:
  - Symmetric erythema over body parts exposed to sunlight, especially neck (Casal's necklace or collar rash).
  - Dermatitis—A. Acute dermatitis characterised by vesiculation cracking, exudation, crusting and ulceration.
  B. Chronic dermatitis characterised by roughening, thickening and brown pigmentation of skin.
- Alimentary tract involvement:
  - Anorexia, nausea, dysphagia, glossitis, angular stomatitis, cheilosis and diarrhoea.

Management

- Oral 100 mg nicotinamide every 6 hours.
- Nutritious diet and high-protein diet.
- Supplementation of other vitamin B complex with iron and folic acid.

Q. Give a brief account of fluorosis.

- This occurs when water fluoride content is high (>3 to 5 ppm).
- It is estimated that more than 62 million people in India suffer from dental, skeletal and non-skeletal fluorosis.
- Dental fluorosis.
  - Mottling of teeth where the enamel loses its lustre, becomes rough, pigmented, pitted and brittle (fluorotic teeth).
  - Later, the teeth become hard and brittle.
- Skeletal fluorosis.
  - Sclerosis of bones, especially of spine, pelvis and limbs.
  - Ligamental calcification, calcification of interosseous membrane and calcification of tendinous insertions.
  - In early stages, pain in bones and joints, muscle weakness and stiffness of joints
  - Later, osteoporosis.
  - Finally, vertebrae fuse.
- Weakness, anaemia, weight loss, brittle bones and stiff joints.

Q. Describe angular stomatitis.

- This refers to cracking of the epithelium at the edges of the lips. Angular stomatitis may be caused by:
  - Iron deficiency anaemia.
  - Riboflavin deficiency.
  - Pyridoxine (B6) deficiency.
  - Niacin deficiency.
  - Herpes labialis at the angle of mouth.
- Angular stomatitis is associated with cheilosis in niacin deficiency and pellagra.

Q. Write a short note on causes, risk factors and treatment of obesity.

- The term obesity implies excess of adipose tissue measured by the following:
  - Body mass index (BMI). It is defined as person's weight (kg) divided by the square of person's height (metres). WHO has recommended following standards for definitions of obesity and other terms:
    - Obesity: BMI >30 kg/m².
    - Overweight: BMI 23.1–29.9 kg/m².
    - Normal: BMI 18.5–23 kg/m².
    - Underweight: BMI <18.5 kg/m².
  - Ideal body weight for height. Calculated by multiplying square of height in meters by 22.5.
    - Overweight: More than 10% of ideal body weight.
    - Obesity: More than 20% of ideal body weight.
    - Underweight: Less than 20% of ideal body weight.
  - Skin fold thickness.
    - Estimated by using special calipers.

- Skin fold thickness measured over triceps, biceps, subscapular and suprailiac regions.
- Normal triceps skin fold thickness in males—12.5 mm.
- Normal triceps skin fold thickness in females—16.5 mm.
● Waist circumference and waist to hip ratio.
- Waist measurement at the narrowest segment between ribcage and iliac crests. Waist circumference >80 cm in females and >90 cm in males indicate abdominal obesity.
- Maximum measurement over buttocks as hip measurement.
- Waist:hip ratio <0.8 in females and <0.9 in males—normal.
- Waist:hip ratio >0.8 in females and >0.9 in males—abnormal.

Causes

Simple obesity	Secondary obesity
● Physical inactivity ● Eating habits ● Psychological factors (overeating may be a symptom of depression, anxiety and frustration) ● Genetic factors	● Hypothyroidism ● Cushing's syndrome ● Hypothalamic disorders ● Diabetes mellitus ● Pickwickian syndrome ● Laurence-Moon-Biedl syndrome ● Medications—valproic acid, carbamazepine, antidepressants, corticosteroids, antipsychotics, lithium and glipizide

Genetic Factors

Role of Leptin

● Leptin is a hormone produced by cells of adipose tissue. It controls food intake and energy expenditure. It acts on leptin receptors (expressed in specific regions of the hypothalamus) to activate and regulate mRNA expression of key hypothalamic neuropeptides, [e.g. pro-opiomelanocortin (POMC)].
● A defect in leptin gene or its receptor may produce obesity.
● Of obese persons, some have a low level of leptin in the blood while majority have high leptin levels indicating peripheral resistance to its actions.
● Defective leptin gene or leptin receptor may be responsible for only a minority of patients with obesity.

Lipoprotein Lipase

● Synthesised by adipocytes.
● Induces obesity by causing deposition of fat in adipose tissue.
● An uncommon cause of obesity.

Risks Associated with Obesity

● Coronary artery disease ● Type 2 diabetes mellitus and insulin resistance ● Hypertension ● Stroke ● Breast, endometrial and colon cancers ● Varicose veins ● Depression	● Dyslipidaemia ● Cholelithiasis ● Sleep apnoea syndrome ● Osteoarthritis ● Increase in all-cause mortality ● Deep vein thrombosis

Treatment

Goals

● Attempt initially to reduce weight by approximately 10% from baseline. Further weight reduction is attempted after initial success.
● Reduce weight at a rate of about ½–1 kg per week for 6 months.

Dietary Therapy

Low-Fat Diet

- Encourage low-calorie diets with low fat. The reduction is usually to the tune of about 500 calories per day.
- Reducing fat alone without reducing total calories is not sufficient.
  - Low-fat diets have a lower energy density than high-fat diets, and as humans respond mostly to volume of food eaten rather than calories, this should lead to a lower energy intake.
  - Low-fat diets also have higher fibre content and this may also enhance satiety.
- Unfortunately, many patients cannot maintain low-fat diet for long time.

Very Low Carbohydrate Diet or Atkins Diet

- Use of very low carbohydrate diet but, with normal or high saturated fats.
- Found to produce loss of weight equivalent to that produced by low-fat diet but there is no data beyond 1 year.
- These diets work by reducing caloric intake by removing a wide range of carbohydrate-rich foods.
- LDL cholesterol may rise by about 2–3%.
- Constipation is another problem.

High-Protein Diet

- It makes use of the increased satiating effect of protein with reduction in carbohydrate. Fat is kept low at 30%.
- These high protein-low carbohydrate diets induce fat burning and mild ketosis, which results in suppression of hunger and promotion of satiety.
- Patients with impaired renal function have a greater decline in renal function with a greater protein intake.
- High dietary protein intake increases urinary calcium excretion with potential risk for bone loss and calcium stone formation.
- Increased risk of colorectal cancer, if increased amount of red meat is consumed.

Physical Exercise

- It reduces abdominal fat and increases cardiorespiratory fitness.
- Moderate exercise should be done for 30–45 minutes/day and 3–5 days a week.

Behaviour Modification

- It is a useful adjunct to diet and physical exercise.
- Patients often require motivation to lose weight.

Pharmacotherapy

- Dietary therapy, physical exercise and behaviour modification should be considered before using drugs.
- Drugs may be used if BMI $\geq$30 kg/m^2.
- Drugs may also be used, if BMI is 27–30 kg/m^2 and the patient has an increased risk:
  - Asian ethnicity.
  - Overweight/obesity-related disease likely to improve with weight loss, such as type 2 diabetes, obstructive sleep apnoea and dyslipidaemia of obesity.
- The patient should be monitored for safety throughout.
- If patient has not lost at least 5% of their body weight by week 12 of using drugs, consider for discontinuation.
- Currently approved drugs are orlistat and lorcaserin and phentermine-topiramate combination.

Sibutramine

- Centrally acting noradrenaline and serotonin uptake inhibitor.
- Suppresses appetite.
- Along with lifestyle modification provides a mean weight loss of approximately 4.5 kg at 1 year.
- Dose is 10–15 mg/day.
- Side effects include dry mouth, constipation, headache and insomnia.
- Produces a dose-related increase in heart rate and may increase blood pressure and cardiovascular events
- Withdrawn due to cardiovascular effects.

Orlistat

- Binds to intestinal and pancreatic lipases in the gut, reducing absorption of dietary triglycerides, cholesterol and fat-soluble vitamins.

- Dose 120 mg three times per day with meals.
- Produces favourable changes in total cholesterol, LDL cholesterol levels, free fatty acids, HbA1c and insulin sensitivity.
- Side effects include oily stools, faecal urgency, diarrhoea, flatulence, faecal incontinence, bloating and abdominal pain that can be minimised by a low-fat diet.
- Fat malabsorption increases the risk of vitamin D, E and β-carotene deficiency. Daily fat-soluble vitamin supplementation is recommended that should be taken between meals.

Rimonabant

- Endocannabinoid-CB(1) blocking drug that has both central and peripheral actions to reduce weight and weight-related metabolic factors such as increasing adiponectin and reducing circulating free fatty acids.
- Side effects include nausea, diarrhoea, anxiety and depression (including increased suicidal risk).
- Withdrawal due to serious side effects.

Lorcaserin

- Approved to be used as an adjunct to a reduced-calorie diet and physical activity for chronic weight management.
- Acts by activating serotonin 2C receptor in the brain, which results in increased satiety and decreased hunger.
- Dose, 10 mg twice a day.
- Cautions should be taken in patients, who are taking serotonergic medications. This can lead to serotonin syndrome. In diabetic patients, hypoglycaemia may occur.
- Side effects include headache, fatigue, nausea, dry mouth, dizziness and constipation.

Phentermine-Topiramate

- This combination has been approved for use in obese patients along with dietary restrictions and lifestyle modifications.
- Topiramate is contraindicated in pregnancy; hence it is recommended that pregnancy testing is done before starting the medication and then every month to ensure patients are not pregnant while taking the medication.
- The combination worsens depression and suicidal ideation; it can also cause mood disorders, anxiety and insomnia.

Others

- Four sympathomimetics agents are approved for short-term use. These are phentermine, diethylpropion, benzphetamine and phendimetrazine.
- These agents produce a modest weight loss benefit by causing early satiety.
- Contraindicated in patients with coronary heart disease, hypertension, hyperthyroidism, and in patients with a history of drug abuse.

Surgery

- Known as bariatric surgery.
- Useful in patients with BMI ≥ 40 kg/m^2 when other methods have failed, and patients with BMI ≥ 35 kg/m^2 who have identifiable medical, physical or psychosocial problems associated with their obesity.
- Perioperative mortality varies from 0.05 to 0.5% depending upon the method used.
- Various options include:
  - Jaw wiring (rarely done).
  - Jejunoileal shunt.
    - Produces significant long-term adverse events such as dehydration, electrolyte imbalance, calcium oxalate renal stones, cirrhosis and protein-calorie malnutrition.
    - Rarely done presently.
  - Gastroplasty or sleeve gastrectomy.
  - Gastric bypass by retrocolic gastrojejunostomy (Roux-en-Y gastric bypass).
  - Laparoscopic adjustable gastric banding.
    - Involves laparoscopic placement of an inflatable silicone band at the very top of the stomach leaving a small gastric pouch that fills quickly and empties slowly. This induces a sense of satiety after consuming smaller amounts of food and a feeling of not being hungry.
    - The balloon of the band is connected to a subcutaneous access port. This allows adding or removing fluid to the system, control of how tight the band is and therefore, how much food can be consumed.
    - Safest, least invasive and most effective procedure.
  - Liposuction.
    - Results in a significant reduction in fat mass and weight, it does not improve insulin sensitivity or risk factors for coronary heart disease.

Chapter 12
Psychiatry

Q. Give a brief account on psychosis.

- Presence of mental state where appreciation of reality is impaired, as evidenced by the presence of psychotic symptoms such as delusions, hallucinations, mood disturbance and bizarre behaviour.
- Includes schizophrenia and mood disorders.

Clinical Features

- **Positive symptoms**
  - Delusions and hallucinations
  - Formal thought disorder
- **Negative symptoms**
  - Flat affect
  - Poverty of thought
  - Lack of motivation
  - Social withdrawal

- **Cognitive symptoms**
  - Distractibility
  - Impaired working memory
  - Impaired executive function
- **Mood symptoms**
  - Depression
  - Elevation (mania)
- **Anxiety/panic/perplexity**
- **Aggression/hostility/suicidal behaviour**

Hallucinations

- Hallucinations mean things that are not really there.
- Auditory hallucinations: Hearing voices of people talking to the patient even when there is no one nearby.
- Thought insertion: Feeling that thoughts are being put into patient's mind.
- Thought withdrawal: Feeling that thoughts are being taken out of patient's mind.
- Thought broadcasting: Feeling that other people are aware of patient's thoughts.

Delusions

- Delusions are beliefs that are maintained despite obvious evidence to contrary.
- Delusion of control or passivity: Feeling of under the control or influence of an outside force.
- Delusions of reference: Feeling that programmes on television or radio hold special meaning for the patient.
- Delusions of persecution: Feeling that patient is being singled out for special treatment or there is a conspiracy against the patient.
- Delusions of grandeur: Feeling special, with unusual abilities or power.
- Delusions of guilt: Feeling that the patient has sinned or has done something deserving punishment.

Differential Diagnosis
Other Causes of Psychotic Symptoms

- Amphetamines/stimulants
- Hallucinogens
- Cannabis
- Temporal lobe epilepsy
- Central nervous system infections (e.g. HIV)
- Huntington's disease
- Cerebral trauma

- Cerebrovascular disease
- Brain tumours
- Cushing disease, use of steroids
- Thyrotoxicosis
- Hyperparathyroidism
- Systemic lupus erythematosus
- Wilson disease

Q. Discuss the aetiology, clinical manifestations and management of schizophrenia.

Q. Write a short note on positive symptoms of schizophrenia and first-rank symptoms of schizophrenia.

- Schizophrenia is a group of disorders characterised by perturbations in language, perception, cognition and behaviour.

Aetiology

- A number of factors have been identified that predispose to, or precipitate, or sustain schizophrenia. They are:
  - Schizophrenia can be transmitted genetically.
  - Family environment can influence the course of the illness. A highly emotional family environment contributes to relapses.
  - Psychological stresses like adverse life events.
  - A viral vector or early developmental abnormalities in some cases.
  - Some cases of schizophrenia are associated with increased cerebral ventricular size, indicating that schizophrenia is accompanied by brain atrophy.
  - Schizophrenia syndrome can be associated with temporal lobe epilepsy, Huntington's chorea, cerebral tumours and demyelinating diseases. This is known as symptomatic schizophrenia.
  - Schizophrenia is associated with a functional overactivity in the dopaminergic neuronal systems in the mesolimbic and mesocortical areas.

Types

- There are four major types of schizophrenic disorders—catatonic, disorganised, paranoid and undifferentiated.
- Schizophrenic patients may also be classified as type I or type II.
  - Type I patients have a predominance of "positive" symptoms, normal ventricular size and a good response to antipsychotic drugs.
  - Type II patients have a predominance of "negative" symptoms, increased ventricular size and a poor response to antipsychotic drugs.

Clinical Features

- Clinical manifestations can be considered under three headings; the first-rank symptoms (which strongly suggest a diagnosis of schizophrenia), other symptoms of lower diagnostic significance and the negative symptoms. Groups I and II together form the positive symptoms.

First rank symptoms	Other symptoms	Negative symptoms
• Thought insertion • Thought broadcasting • Passivity feelings • Auditory hallucinations • Delusional perceptions	• Catatonia • Thought disorder • Neologisms • Delusions—grandiose, paranoid, sexual or religious • Visual, tactile, olfactory or gustatory hallucinations • Affective change	• Social withdrawal • Poverty of speech • Flatness of affect

Management

Neuroleptic Drugs (Antipsychotic Drugs)

- It is conventional to start with chlorpromazine 100 mg thrice daily, gradually building up the dose to a maximum of 1500 mg daily or until symptoms subside. Higher doses may be required if the patient is aggressive or agitated.
- When symptoms have improved, it is usual to reduce the dose or change over to long-acting intramuscular neuroleptics (e.g. fluphenazine 20–100 mg or flupenthixol 40–200 mg once in 2 weeks).
- Antipsychotic drugs block both D_1 and D_2 groups of dopamine receptors. This results in high incidence of extrapyramidal features with their use. They also block adrenergic and cholinergic receptors and cause a number of side effects. A rare adverse effect is neuroleptic malignant syndrome.
- Newer antipsychotics include clozapine, risperidone and olanzapine. Though efficacy is similar to older drugs, these are better tolerated.

Social Measures

- These patients do best in an environment that has a regular, and predictable routine. Positive symptoms are exacerbated in highly charged emotional situations while negative symptoms are induced in environments that are understimulating.

Q. What are affective disorders (mood disorders)? How do you classify them?

Q. What are the clues to bipolar disorders?

- The affective (mood) disorders are characterised by a disturbance of mood, either depression or mania.

Classification of Mood Disorders

- The term unipolar disorder is used when recurrences always take a depressive form.
- The term bipolar disorder is used when recurrences are both manic and depressive.
- The affective (mood) disorders can be classified as primary and secondary.
  - The term primary affective disorder is used when the affective episodes (mania or depression) are not secondary to any other psychiatric or physical illness.
  - The term secondary affective disorder is used when the affective episodes are secondary to another psychiatric or physical illness.

Classification of Bipolar Disorders

Bipolar I disorder
- At least one lifetime episode of mania, and usually (but not necessarily) episodes of depression
- May also include episodes of hypomania

Bipolar II disorder
- Episodes of both hypomania and depression. No manic episodes

Clues to Bipolar Disorders

- Feeling energized and "wired"	- Spending money in an unusual manner or inappropriately
- Excessively seeking stimulation	- Indiscreet and disregarding social boundaries
- Needing less sleep	- Having poor self-regulation
- Irritable if stopped from carrying out ideas	- Making excessively creative and grandiose plans
- Disinhibited	- Having difficulty in discussing issues rationally or maturely
- Offensive or insensitive to the needs of others	- Reporting enhanced sensory experiences

Q. Discuss the clinical manifestations and management of depression.

- Depressive disorders are characterised by persistent low mood, loss of interest and enjoyment and reduced energy. They often impair day-to-day functioning.
- Major depressive disorder is characterised by one or more major depressive episodes (i.e. at least 2 weeks of depressed mood or loss of interest accompanied by at least four additional symptoms of depression).

Clinical Features

Psychological

- Depressed (dysphoric) mood is the most characteristic feature. There may be diurnal variation of the mood, the depressed mood being worst in the early morning or in the evening.
- Loss of pleasure in life, and loss of interest in oneself and others.
- Low self-esteem and ideas of hopelessness and worthlessness.
- Self-blame and feelings of excessive or inappropriate guilt.
- Psychotic features (e.g. hallucinations, delusions, etc.) may be present such a condition is known as psychotic depression.

Somatic

- Sleep disturbance may occur as initial insomnia, early morning wakening or hypersomnia.
- Fatigue, headache and various other pains.
- Anorexia, weight loss or weight gain, and constipation.
- Poor concentration, psychomotor retardation and reduced libido.

Diagnosis

1. Depressed mood most of the day, nearly every day as indicated by either subjective report (e.g. feels sad, empty, hopeless) or observations made by others (e.g. appears tearful)
2. Markedly diminished interest or pleasure in all or almost all activities most of the day, nearly every day
3. Significant weight loss when not dieting or weight gain (e.g. a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day
3. Loss of energy or fatigue nearly every day
4. Loss of confidence or self-esteem
5. Recurrent thoughts of death or suicide or any suicidal behaviour
6. Diminished ability to think or concentrate or indecisiveness, nearly every day
7. Unreasonable feelings of self-reproach or excessive or inappropriate guilt, nearly every day
8. Psychomotor agitation or retardation, nearly every day
9. Insomnia or hypersomnia, nearly every day
10. Change in appetite (decrease or increase with corresponding weight change)

Note: 1. Symptoms 1 and/or 2 and any 4 others must be present for at least 2 weeks
     2. Symptoms not caused by a medical condition, a substance or a bereavement

Management

- In acute bipolar depression, a mood stabilizer either alone or in combination with an antidepressant is effective. Mood stabilizer with proven antidepressant effects in bipolar depression include lithium, lamotrigine, quetiapine and olanzapine.
- A tricyclic antidepressant (e.g. amitriptyline) drug was the first choice previously. In those who did not respond to this, a monoamine oxidase inhibitor (MAOI) or mianserin was tried.
- However, at present, selective serotonin reuptake inhibitors (SSRIs) have replaced tricyclic antidepressants as the drugs of choice in the treatment of depressive disorders. These agents are better tolerated and are relatively safer, if taken in overdose. SSRIs include fluoxetine, sertraline, fluvoxamine and citalopram.
- Another agent is venlafaxine that inhibits reuptake of norepinephrine and serotonin.
- Cognitive therapy in combination with antidepressants may be beneficial in some cases.
- Imipramine and sertraline are useful in patients with psychotic depression.
- Electroconvulsive therapy (ECT) is indicated in selected situations—e.g. in those with a high risk of suicide, depressive stupor, psychotic symptoms, and when antidepressants have been ineffective.

Q. What are the clinical manifestations of mania? Give a broad outline of the management.

Q. Define hypomania.

Clinical Features of Mania

- The mood is elevated and expansile with a feeling of well-being.
- High confidence and self-esteem with grandiose ideas.
- Highly energetic with increased motor activity.
- Patient is more talkative than usual, with a pressure to keep talking.
- Thoughts come rapidly and jump from one topic to another (flight of ideas).
- Increased appetite and decreased need for sleep.
- Sexual promiscuity may occur.

Hypomania

- Episodes of pathologically elevated (and/or irritable) mood for at least several days in duration.
- Associated characteristic symptoms and behavioural change indicative of disinhibition, poor judgement, grandiosity and increased speed of thoughts, speech and behaviour.
- Distinctly different from the individual's normal functioning.
- No marked functional impairment, psychotic features or hospitalization.

Diagnosis

1. Abnormally and persistently elevated, expansive or irritable mood
2. Distractibility

3. Indiscretions (e.g. shopping sprees, dangerous sexual activities)
4. Grandiosity
5. Fast thoughts or flight of ideas
6. Activity—increase in goal-directed activity
7. Sleep—decrease in the need for sleep
8. Talkativeness or pressured speech

Note: Symptoms 1 and any 3 others must be present for at least 4 days in mania and for 7 days in hypomania

Management
- Manic attacks can be suppressed with lithium, valproate, carbamazepine or atypical antipsychotic (e.g. olanzapine, aripiprazole, quetiapine or risperidone).
- Also add neuroleptic drugs (haloperidol, chlorpromazine) or benzodiazepines to calm or sedate the mood until the mood stabiliser agent takes effect (about 1 week).
- ECT in resistant cases.
- Lithium carbonate and carbamazepine are useful prophylactically.

Q. How do you classify anxiety disorders? Give a brief account of treatment of anxiety disorders.

Q. Describe panic disorder.

Q. Discuss generalised anxiety disorder.

Q. What is post-traumatic stress disorder (PTSD)?

Q. How do you classify phobic disorders? Give a brief account of these disorders.

Q. Give a brief account of classification of anxiety disorders.

Anxiety states	Phobic disorders
• Panic disorder • Generalised anxiety disorder • Post-traumatic stress disorder (PTSD)	• Agoraphobia • Social phobia • Simple phobia

Panic Disorder
- There are recurrent attacks of severe anxiety that are sudden and unpredictable. During attacks, physical symptoms are prominent and include palpitations, chest pain, breathlessness, sweating, chills, nausea, trembling, fear of dying or losing control, numbness and feeling of detachment. These last for 10–15 minutes.
- May be accompanied by agoraphobia, an avoidance of situations where a person may feel trapped and unable to escape.
- In between attacks, the patient is free of anxiety.

Generalised Anxiety Disorder
- Characterised by excessive worry and anxiety, which are difficult to control, cause significant distress and impairment and occur on more days than not for at least six months.
- Patients have persistent, excessive and/or unrealistic worry associated with other features including muscle tension, impaired concentration, autonomic arousal, restlessness and insomnia. Complaints of tachycardia, dyspnoea and palpitations are rare.
- Symptoms of anxiety are prominent in psychiatric disorders such as depressive illness and schizophrenia. Many physical illnesses like hyperthyroidism, phaeochromocytoma, hypoglycaemia, alcohol withdrawal and temporal lobe epilepsy can mimic anxiety disorders. Hence, these conditions should be excluded before making a diagnosis of generalised anxiety disorder.

Post-Traumatic Stress Disorder (PTSD)
- PTSD is characterised by recurrent bouts of severe anxiety accompanied by vivid reminiscences (or "flashbacks") of the initial traumatic event.

- PTSD stems from exposure to a traumatic event (e.g. a military experience, a physical or sexual assault, a motor vehicle accident, a natural disaster) that involved actual or threatened death or serious injury to oneself or others.
- Typically, patients re-experience the traumatic event (e.g. nightmares, flashbacks), engage in avoidance of stimuli associated with the sentinel trauma (e.g. impaired recall of events related to the trauma), and experience increased autonomic reactivity (e.g. hypervigilance, irritability, insomnia, heightened startle response).
- PTSD is classified as either acute or chronic (or delayed). In acute PTSD onset of symptoms begins within 6 months of trauma or the duration of symptoms is less than 6 months. In chronic (or delayed) PTSD symptoms start more than 6 months after trauma (delayed) or persist for more than 6 months (chronic).

Phobic Disorders

- Phobic disorders comprise a group of disorders having in common persistently recurring, irrational severe anxiety of specific objects, activities or situations with secondary avoidance behaviour of the phobic stimulus.
- Agoraphobia: The individual has marked fear of and thus avoids being alone or being in public places—e.g. crowds, tunnels and bridges.
- Social phobias: These are persistent irrational fears and the need to avoid any situation, where one might be exposed to scrutiny by others and potentially be embarrassed or humiliated. Even the possibility of such a situation evokes an anticipatory anxiety. The individual is aware that this fear is excessive.
- Simple phobia: The individual experiences significant distress, when confronted with the phobic stimulus or even the possibility of confrontation with the phobic stimulus. The individual may experience symptoms identical to those of panic attacks. Common examples include fear of heights (acrophobia), fear of closed spaces (claustrophobia) and fear of animals.

Treatment

- Use of a SSRI—discussed separately. SSRIs increase the availability of serotonin, which is thought to be reduced in anxiety disorders.
- Use of a selective serotonin–norepinephrine reuptake inhibitor (e.g. venlafaxine).
- Anxiolytic agents such as benzodiazepines (e.g. lorazepam, alprazolam, clonazepam) can be used as a temporary adjunct to aid in minimising anxiety, in particular when starting a medication therapy. Their long-term use should be avoided since it may lead to tolerance and increase risk of abuse or dependence.
- Cognitive-behavioural therapy that involves addressing cognitive distortions, psychoeducation, breathing exercises, progressive muscle relaxation and progressive exposure.

Q. Discuss briefly about obsessive compulsive disorder.

- Previously grouped under anxiety disorders.
- Obsessions are persistent intrusive thoughts. Compulsions are intrusive behaviours. Attempts made to ignore or suppress the obsessive thought are usually not successful. The compulsive act is performed with a sense of subjective compulsion coupled with a desire to resist the compulsion. The individual generally recognises the senselessness of the behaviour and does not derive pleasure from carrying out the activity, although it provides a release of tension.
- Examples are repeated checking to be assured that the door was locked, repeated hand washing and extreme neatness.

Treatment

- Psychotherapy.
- Pharmacotherapy.
  - SSRIs including fluoxetine, fluvoxamine and citalopram.
  - Tricyclic antidepressants particularly clomipramine.

Q. Give a brief description of hysteria.

Q. Write a short note on conversion disorder and dissociation disorder.

Q. Explain hysterical amnesia and Briquet's syndrome (somatisation disorder) in brief.

- Hysteria is a syndrome characterised by a loss or distortion of neurological function, not fully explained by organic disease. The patient develops symptoms and signs of illness (mental, physical or both) for some real or imagined gain without really being fully aware of the underlying motive.

- Hysteria is protean in manifestation and may simulate any disease. In psychoanalytic terms, hysteria has been seen as a maladaptive way of coping with an unresolved psychological conflict, i.e. by becoming ill. The patient thus derives primary gain by relieving the conflict and secondary gain by obtaining sympathy and attention from others or by avoiding everyday responsibilities.

Clinical Features

- Two main variants of hysteria are conversion disorder and dissociation disorder.

Conversion Disorder

- The symptoms mimic lesions of the motor or sensory nervous system. There is apparent unconcern (la belle indifference) even in the face of gross physical disability. Common presentations are gait disturbances, loss of function in limbs, aphonia, pseudoseizures, sensory loss and blindness.

Dissociation Disorder

- Hysterical amnesia usually develops acutely. The memory loss is patchy and inconsistent. A characteristic feature is a loss of personal identity so that the patient is unable to recall his name, address or other personal and family details. Amnesia occurs to escape from intolerable anxiety and distress about some problem or difficulty or situation in which the patient finds himself.
- Briquet's syndrome (somatization disorder) is a chronic condition almost entirely confined to females, which begins before the age of 30. The cardinal features are multiple and recurrent somatic complaints affecting many organ systems for which medical attention is sought.

Q. Describe Munchausen's syndrome.

- This is a factitious disorder named after the German Baron von Munchausen who was legendary for his inventive lying.
- The disorder is commonly seen in males. The patient changes his name frequently, and usually has a record of various medical reports with history of "doctor shopping".
- He fabricates a convincing history and presents to the doctor with dramatic symptoms of a medical emergency.
- He usually seeks medical attention at night when junior doctors or residents are on duty.
- He persuades an inexperienced doctor or internee to undertake complicated investigations or exploratory surgery.
- Abdomen may show a "surgical battlefield"—i.e. several scar marks due to previous operations.

Q. What are the common symptoms and signs of substance abuse? List down the investigations required.

- Substance abuse is defined as psychological dependence and heavy consumption of a substance, despite social and occupational problems.
- Substance dependence is defined as similar impairment with increased tolerance or presence of physical signs on withdrawal of substance.
- The substances most commonly abused are alcohol, diazepam, tranquillisers, barbiturates, nicotine (smoking), cocaine, amphetamines, heroin, glue, etc.

Common Symptoms and Signs Suggesting Substance Abuse

Symptoms	Signs
• Frequent absences from school or work	• Tremors
• History of frequent trauma	• Odour of alcohol on breath
• Depression or anxiety	• Conjunctival injection
• Labile hypertension	• Labile hypertension
• Epigastric distress, diarrhoea	• Tachycardia
• Sexual dysfunction	• Tender hepatomegaly
• Sleep disorders	

- Acute presentation may be due to overdose, withdrawal, accident injuries.

Laboratory Investigations

- A urine screen for alcohol and other substances of abuse.
- The most useful investigations to confirm alcohol abuse are:
  - Gamma-glutamyl transpeptidase (GGT) is the most sensitive assay for alcohol abuse. It is elevated in such patients.
  - Elevated mean corpuscular volume (MCV), but is less sensitive than GGT.
  - Elevated carbohydrate deficient transferrin level is highly specific in the absence of liver disease.

Q. Give a brief account of alcohol dependence.

- A chronic disorder caused by genetic, psychosocial and environmental factors.

Laboratory Investigations

- See above.

Treatment

- Two phases: detoxification and rehabilitation.

Detoxification

- Deals with acute withdrawal symptoms and therefore, requires use of medications.
- Approved medications include naltrexone, disulfiram and acamprosate.

Disulfiram

- Alcohol is converted to acetaldehyde by alcohol dehydrogenase which is further broken down by the enzyme acetaldehyde dehydrogenase. Disulfiram acts as a deterrent to drinking by inhibiting the enzyme aldehyde dehydrogenase, thereby increasing the levels of toxic substance, acetaldehyde in the body.
- If patient consumes alcohol while on disulfiram, acetaldehyde accumulates that leads to flushing, palpitations, nausea, faintness, and in some cases collapse.
- Initial dose is 250 mg a day that can be increased to a maximum of 500 mg after a few days.
- Should not be given to patients with serious active liver disease or cardiovascular disorders, to pregnant females or patients with suicidal tendencies.
- It also interferes with the metabolism of other drugs, most notably tricyclic antidepressants, MAOI, heparin and some anticonvulsants.
- Severe adverse reactions are rare and include myocardial infarction, congestive heart failure, respiratory depression, convulsions and death.

Naltrexone

- An opioid receptor antagonist that reduces the feelings of cravings. It also reduces the severity of relapse particularly over a short term.
- Dose is 50 mg/day in a single dose.
- . Side effects include nausea and headache.
- Long-term opioid therapy for chronic pain or heroin dependence is a contraindication for naltrexone because the drug could precipitate severe withdrawal syndrome.
- Also contraindicated in patients with liver disease. Liver function tests should be done every month in the initial few months of treatment.

Acamprosate

- Normalises the dysregulation of N-methyl-D-aspartate (NMDA)-mediated glutamatergic excitation that occurs in alcohol withdrawal and early abstinence. This reduces cravings.
- Dose is 1998 mg/day if weight >60 kg and 1332 mg/day if weight <60 kg. Available in 333 mg enteric-coated tablet and is to be given thrice a day.
- Side effects: diarrhoea, dizziness and headache.
- Use cautiously in patients with renal impairment.

Rehabilitation

- Helps to prevent relapse and development of lifestyle compatible with long-term abstinence.
- Requires psychotherapeutic interventions.

Q. Discuss alcohol withdrawal in brief.

● Alcohol withdrawal in a chronic alcoholic person is characterised by sudden exhibition of central nervous system excitation.

Clinical Features

● These develop 6–48 hours after the reduction of ethanol intake and may last for 2–7 days.

Minor Withdrawal Symptoms

● Minor withdrawal symptoms include insomnia, tremors (the shakes), hyperreflexia, mild anxiety, gastrointestinal upset, headache, diaphoresis, tachycardia, palpitations, hypertension and anorexia. These features resolve within 24–48 hours.

Alcoholic Hallucinosis

● This refers to hallucinations that develop within 12–24 hours of abstinence and resolve within 48–72 hours.
● Hallucinations are usually visual, although auditory and tactile phenomena may also occur. In contrast to delirium tremens, alcoholic hallucinosis is not associated with clouding of the sensorium.

Withdrawal Seizures

● Withdrawal-associated seizures or "rum fits" are generalised tonic–clonic convulsions that usually occur within 7-48 hours after the last drink, but may occur after only 2 hours of abstinence. Seizures have little or no postictal period.
● Approximately, 3% of chronic alcoholics have withdrawal-associated seizures and, of those patients, 3% develop status epilepticus.
● Approximately one-third of patients, who develop delirium tremens have a preceding alcohol withdrawal seizure.

Delirium Tremens

● It typically begins between 48 and 96 hours after the last drink and lasts 1–5 days. If early alcohol withdrawal features are not treated, about 5% of patients will progress to delirium tremens.
● Clinical features include hallucinations, disorientation, tachycardia, hypertension, low-grade fever (sometimes high-grade), agitation, diaphoresis and dilated pupils.
● Patients may be dehydrated as a result of diaphoresis, hyperthermia, vomiting and tachypnoea.
● Hypokalaemia, hypomagnesaemia and hypophosphataemia are common.
● Death occurs in 5% of cases and is usually due to arrhythmias, pneumonia or electrolyte imbalance.

Differential Diagnosis

● The alcohol withdrawal syndrome can be confused with several conditions like encephalitis, drug-induced psychosis, hypoglycaemia (alcohol induced), anticholinergic intoxication and withdrawal of sedative-hypnotics.
● Opioid withdrawal is associated with a normal mental status, no fever and infrequent seizures.
● Withdrawals associated with barbiturates and benzodiazepines usually progress slowly and the frequency of seizures is higher that tend to appear later, generally around seventh day compared to around second day in alcohol withdrawal.

Management

● Always consider a possibility of associated conditions like pneumonia, GI bleed, liver failure, pancreatitis, electrolyte imbalance, neurological injury, hypothermia or hyperthermia and trauma.
● Maintain airway and breathing.
● Administer thiamine and glucose intravenously after withdrawing appropriate blood samples in patients with altered sensorium.
● In mild cases of withdrawal, provides supportive care in the form of reassurance and nursing care with frequent monitoring of vital signs. Fluid and electrolyte imbalance should be corrected.
● Benzodiazepines (diazepam and lorazepam) are required in patients with moderate to severe withdrawal. These are also useful in controlling seizures.
● β-blockers help in reducing anxiety and tremors.
● The utility of magnesium in patients with alcohol-related seizures is controversial. Antiepileptics like phenytoin, valproic acid, and levetiracetam are of little use in treating or preventing alcohol withdrawal seizures.

Q. Describe smoking and its health risks.

Q. Name the drugs useful to reduce nicotine dependence.

Contents of Cigarette Smoke

- More than 4000 substances in cigarette smoke.

Category	Components
• Carcinogens	Tar
	Polynuclear aromatic hydrocarbons
	N-nitrosonornicotine
	Benzopyrene
	Trace metals—nickel, arsenic, polonium, etc.
	Nitrosamine
	Hydrazine
	Vinyl chloride
• Co-carcinogens	Phenol
	Cresol
	Catechol
• Addicting agent	Nicotine
• Other	Carbon monoxide

- Main stream smoke—smoke emerging from mouthpiece during puffing.
- Side stream smoke—smoke emitting between puffs at the burning end and from mouth end. Contains more carcinogens compared to main stream smoke.

Smoking Index and Pack-Years

- Smoking index is the number of cigarettes per day multiplied by total duration of smoking in years. If a person smokes 10 cigarettes/day for the past 15 years, his smoking index is 150.
    - Smoking index <100—mild smoker.
    - Smoking index 100–300—moderate smoker.
    - Smoking index >300—heavy smoker.
- Pack-years is number of packs of cigarettes per day multiplied by total duration of smoking in years (1 pack = 20 cigarettes).
    - Risk of developing lung cancer is 40 folds in persons with pack-years of 40.

Passive Smoking

- Also known as second hand smoking, involuntary smoking and environmental tobacco smoke exposure.
- Occurs when smoke from one person's burning tobacco product i.e. side stream smoke or exhaled smoke is inhaled by others.
- Passive smoking increases risk of cancers, CAD, respiratory illnesses and death.

Pharmacology of Smoke

- Nicotine is the main toxic substance producing acute effects as well as dependence.
- Inhalation of nicotine produces:
    - Increase in both systolic and diastolic blood pressures.
    - Increase in heart rate.
    - Increase in force of myocardial contraction.
    - Increase in excitability of myocardium.
    - Increase in myocardial oxygen consumption.
    - Peripheral vasoconstriction.
- Inhalation of carbon monoxide leads to polycythaemia and CNS impairment.
- Carcinogens increase the occurrence of several cancers.
- Smoking impairs ciliary movement in respiratory tract, inhibits function of alveolar macrophages and produces hyperplasia and hypertrophy of mucus-secreting glands. The airway resistance is increased due to smooth muscle contraction

via stimulation of submucosal irritant receptors. It also inhibits antiproteinases and stimulates neutrophils to release proteolytic enzymes.

Health Effects of Chronic Smoking

- Cancers
  - Lung
  - Oral cavity
  - Larynx
  - Oesophagus
  - Stomach
  - Urinary bladder
  - Kidney
  - Colon
  - Cervix
  - Acute myeloid leukaemia
- Coronary artery disease
- Strokes
- Chronic obstructive lung disease
- Aortic aneurysm
- Peripheral vascular disease
- Periodontitis
- Infertility

- All forms of tobacco smoking including cigarettes, cigars, pipes, bidis and hookahs can produce ill health effects and addiction.
- Cigar and pipe smokers tend to inhale less smoke than cigarette smokers, so their risk of lung cancer is lower but is still several times higher than the risk for non-smokers.
- Occurrence of carcinoma of oral cavity, larynx and oesophagus is same with cigar, pipe and cigarette.
- There is no evidence that "low-tar" cigarettes produce less ill-effect in humans.

Smoking and Cardiovascular Disease

- Major risk factors for CAD include smoking, hypertension and hypercholesterolaemia. Presence of all three risk factors increases risk of CAD eight folds.
- Deaths due to CAD are 60% higher in smokers compared to non-smokers.
- People under 40 are five times more likely to have a heart attack if they smoke.
- Sudden death is two to four times more common in smokers.
- Females who smoke are also predisposed to CAD.
- Cerebrovascular accidents more common in smokers.
- Peripheral vascular diseases more common in smokers.

Smoking and Respiratory Diseases

- Abnormalities in pulmonary function tests include elastic recoil and small airway functions.
- Chronic obstructive lung disease is about 10–20 times greater in smokers.
- Male smokers have 4–25-folds higher mortality due to chronic obstructive lung disease than non-smokers.
- Increased incidence of influenza infection in smokers.
- Cancers of larynx and lung common in smokers.

Smoking and Gastrointestinal Tract

- Smoking produces discolouration of teeth, and reduced taste and smell.
- Peptic ulcers (both gastric and duodenal) are more common. Also impairs ulcer healing.
- Increased prevalence of cancers of oral cavity, oesophagus, stomach, colon and pancreas.

Smoking and Pregnancy

- Smoking reduces chances of conception.
- Smoking during pregnancy produces intrauterine growth retardation leading to reduced weight of newborn.
- Rates of spontaneous abortion, intrauterine foetal death and sudden infant death higher in smokers.

Nicotine Withdrawal

- Withdrawal symptoms in chronic users begin to appear approximately 30 minutes after every dose.
- Features include confusion, restlessness, anxiety, insomnia, dizziness, depression, feelings of frustration and anger, nightmares, poor concentration, headache and increased appetite.

Smoking Cessation

- Nicotine replacement therapy.
  - Use of nicotine patches, nicotine gums, lozenges and nasal sprays.
  - Contraindicated in unstable coronary artery disease, untreated peptic ulcer disease, recent MI and recent stroke.
  - Method of gum use:
    - Chew slowly until a strong taste or tingling sensation felt.
    - Stop chewing and place the gum between cheek and gums.
    - Chew again when intensity of tingling decreases.
    - Repeat this cycle of "park and chew" for about 30 minutes, or until tingling sensation subsides.
- Bupropion.
  - An antidepressant that is chemically unrelated to tricyclic antidepressants or SSRIs.
  - The mechanism of action is unknown; however, it is a non-competitive antagonist of nicotine receptors and inhibits reuptake of dopamine, noradrenaline and serotonin in CNS.
  - Dose is 75–150 mg twice a day.
  - Side effects include dry mouth, insomnia and skin rash.
  - Rarely, can precipitate seizures.
- Varenicline.
  - A partial agonist at the α4β2 nicotinic acetylcholine receptor.
  - It is possibly more effective than nicotine and bupropion.
  - Contraindicated in pregnancy and lactation.
  - Side effects include nausea, insomnia, abnormal dreams, neuropsychiatric symptoms (agitation, depressed mood, suicidal ideation), visual disturbances and alteration in consciousness.
- Other medicines.
  - Clonidine and nortriptyline.
- Electronic cigarettes.
  - A battery-powered vaporiser which contains nicotine derived from tobacco plant and gives the feeling of smoking a cigarette.
  - Have a heating element which vaporises the liquid solution containing nicotine and other substances some of which are toxic.
  - They possibly reduce various health effects of cigarette smoking.
  - However, potential risks of e-cigarettes, how much nicotine or other potentially harmful chemicals are being inhaled during use, and whether there are any benefits associated with using them are not clear.

Q. What are the commonly used antipsychotic drugs and their uses?

- The antipsychotic drugs are used in schizophrenia, mania and acute confusion.

Antipsychotic Drugs

Group	Drug	Usual dose (mg/day)
• Phenothiazines	Chlorpromazine	100–1500
	Thioridazine	50–800
	Trifluoperazine	5–30
	Fluphenazine	5–15
• Butyrophenones	Haloperidol	5–30
	Droperidol	5–10*
• Thioxanthenes	Flupenthixol	40–200**
• Diphenylbutylpiperidines	Pimozide	4–30
• Benzamides	Sulpiride	600–1800
• Dibenzodiazepine	Clozapine	200–600
	Quetiapine	300–600
• Benzisoxazole	Risperidone	2–6
• Thienobenzodiazepine	Olanzapine	10–30

*mg intramuscularly
**mg fortnightly intramuscularly

- Phenothiazines, butyrophenones and thioxanthenes are known as typical antipsychotics while others as atypical antipsychotic agents. The latter group of agents produce less of extrapyramidal side effects as compared to typical ones.

Q. What are the commonly used antidepressant drugs? What are their other indications?

- Antidepressant drugs are useful in depressive illness, obsessive compulsive disorders and phobic disorders.

Antidepressant Drugs

Group	Drug	Usual dose (mg/day)
• Tricyclics	Amitriptyline	75–150
	Imipramine	75–150
	Dothiepin	75–150
	Clomipramine	75–150
• Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine	20–60
	Fluvoxamine	100–200
	Sertraline	50–200
	Citalopram	10–60
	Escitalopram	5–30
• Tetracyclics	Mianserin	30–90
• Atypical antidepressants	Bupropion	300–450
	Mirtazapine	15–45
• MAOI (rarely used)	Phenelzine	60–90
	Tranylcypromine	20–40
• Serotonin and norepinephrine reuptake inhibitors	Venlafaxine	150–300
	Duloxetine	60–120

Q. Discuss electroconvulsive therapy (ECT).

- Involves the administration of high voltage, brief and direct current impulses to the head to induce seizures in brain while the patient is anaesthetized and paralysed. Electrodes can be placed bilaterally or unilaterally over the nondominant hemisphere.
- ECT is safe with few side effects. Headache, Postictal confusion, a short retrograde and antegrade amnesia can occur.
- ECT is mainly useful in depressive illness, but also in selected cases of mania and acute schizophrenia.

Indications for ECT in Depressive Illness

- Severe depression with paranoid or nihilistic delusions
- High suicidal risk, where quick response is needed
- Failure to respond to a tricyclic and an alternative antidepressant
- Depressive stupor
- Inability to tolerate the side effects of antidepressants

Q. Discuss briefly common sleep disorders.

- Various sleep disorders are:
    - Insomnia
    - Sleep related breathing disorders
    - Narcolepsy
    - Circadian rhythm disorders
    - Parasomnias
    - Sleep related movement disorders

Insomnia

- Inability to sleep or maintain sleep, despite the patient having adequate opportunity and circumstances to sleep, when associated with impairment of daytime functioning or mood symptoms.

- Patients may complain of difficulty falling asleep (sleep onset insomnia) or difficulty remaining asleep (sleep-maintenance insomnia) with frequent nocturnal awakenings or early morning awakenings associated with non restorative sleep.
- Insomnia can heighten the perception of pain and may be associated with development of endocrine disturbances. It also has an association with increased risk for hypertension or cardiovascular disease. Insufficient sleep can lead to increased risk for motor vehicle accidents and occupational errors.

Causes

- Primary (idiopathic).
- Depression, anxiety or somatoform disorder.
- Medication or substance use, including stimulants, corticosteroids, caffeine, alcohol, etc.
- Medical conditions including chronic pain, chronic obstructive pulmonary disease, asthma, menopause, nocturia and neurologic disorders.

Treatment

- Cognitive behavioural therapy.
- Pharmacologic therapy:
  - Triazolam, zolpidem and ramelteon (a melatonin receptor agonist) for sleep onset insomnia.
  - Estazolam and eszopiclone for sleep-maintenance insomnia.
  - Zaleplon and sustained-release zolpidem for both sleep onset and sleep-maintenance insomnia.

Narcolepsy

- It is excessive daytime sleep that a patient cannot resist.

Diagnosis

- Severe excessive daytime sleepiness occurring almost daily for at least 3 months that interfere with functioning.
- Rapid eye movement (REM) intrusion phenomena that includes:
  - Cataplexy—sudden self-limited episodes of loss of muscle tone when patient is awake, which is usually triggered by laughter or other strong emotions.
  - Hypnagogic hallucinations—vivid and often frightening perceptual hallucinatory experiences, which occur during the transition between waking and sleep.
  - Sleep paralysis—occurs as the patient transitions from sleep to waking, and consists of episodes up to several minutes in duration of inability to move and occasionally feeling unable to breathe despite being awake.
- Electrographic evidence:
  - An abnormal multiple sleep latency test done during day, with a sleep latency of 8 minutes or less.
  - At least two sleep onset REM periods on polysomnography (normally, REM sleep occurs 60–90 minutes after onset of sleep).

Treatment

- Modafinil, a wakefulness-promoting drug is useful. It has low addiction potential.
- Sodium oxybate, a sodium salt of γ-hydroxybutyrate is administered at night to help consolidate REM sleep and increase slow-wave sleep. It significantly reduces daytime sleepiness and also improves cataplexy.
- Others: Selegiline (a monoamine oxidase-B inhibitor), clomipramine, fluoxetine and venlafaxine.

Circadian Rhythm Sleep Disorders

- Chronic or recurring sleep disturbances (insomnia or hypersomnia) are because of misalignment between their endogenous circadian timing and external influences.
- Common types:
  - Delayed sleep phase type—sleep and wake times are later than desired, often resulting in daytime sleepiness, when conventional waking times are enforced.
  - Advanced sleep phase type—sleep and wake times are earlier than desired.
  - Jet lag—transient symptoms of difficulty falling asleep at the appropriate time and daytime sleepiness following rapid change in time zones altering the timing of exogenous light stimuli.

Diagnosis

- Based on history and a sleep diary.
- Actigraphy—based on a wrist-mounted motion detector worn as an outpatient for at least 7 days that can help to quantify time spent asleep.

Treatment

- Bright light therapy—exposure to bright light around 2500 lux for 2 to 3 hours in the mornings.
- Chronotherapy—useful in delayed sleep phase type of circadian rhythm disorders; patient delays sleep 3 hours every 2 days until he/she adjusts to the conventional sleep and wake time.
- Melatonin—administered in the afternoon or evening in patients with delayed sleep phase.
- For jet lag:
  - Behavioural strategies (good sleep hygiene, shifting sleep and wake times gradually before travel to conform to the destination's time zone and avoiding bright light exposure before bedtime).
  - Melatonin administered before bedtime in the new time zone.

Parasomnias

- Undesirable experiences or behaviours that occur during transitions between sleep and waking.
- Represent central nervous system activation and intrusion of wakefulness into sleep, producing non-volitional motor, emotional or autonomic activity.
- Non-REM sleep parasomnias include confusional arousals and sleep terrors. Sleep terrors are dramatic sudden arousals from non-REM sleep with associated screaming, fear and increased autonomic activity; patients may be disoriented, unresponsive to the environment and typically do not remember the event afterward.
- REM sleep associated parasomnias include nightmares and behaviour disorders. Nightmares typically occur towards the end of night and are not associated with autonomic activity or amnesia. Behaviour disorders consist of abnormal loss of muscle tone inhibition during REM sleep, permitting vigorous movements while dreaming. Sleep behaviours can include screaming, punching and kicking for up to several minutes, sometimes resulting in injury to the patient or bed partner. Polysomnography shows anomalous increase in muscle tone on electromyogram during REM sleep.

Treatment

- Avoid serotonin reuptake inhibitors, MAO inhibitors, caffeine or alcohol.
- Remove dangerous objects from the sleep environment.
- Drugs include clonazepam, tricyclic antidepressants, dopamine agonists or levodopa, carbamazepine and melatonin.

Sleep Related Movement Disorders

- Include restless leg syndrome and periodic limb movement disorder.

Restless Leg Syndrome

- An overwhelming urge to move legs, usually accompanied by an uncomfortable sensation.
- May disrupt sleep initiation.
- Rest or inactivity exacerbates the urge to move the legs.
- Physical activity temporarily relieves the urge to move the legs.
- Symptoms more prominent in the evening or nighttime that may disrupt sleep initiation.
- May be secondary to pregnancy, end-stage renal disease, iron or folate deficiency, peripheral neuropathy, radiculopathy, rheumatoid arthritis or fibromyalgia.
- Certain drugs like antihistamines, dopamine receptor antagonists and antidepressants (with the exception of bupropion) may exacerbate it.
- First-line drugs are dopaminergic medications (ropinirole, pramipexole). Others include gabapentin, benzodiazepines, clonidine or opiates.

Periodic Limb Movement Disorder

- Symptoms include repetitive, stereotyped limb movements occurring in non-REM sleep, typically involving the lower limbs.
- Occur every 20–30 seconds.
- Movements often disrupt sleep and lead to daytime sleepiness.
- Treatment is similar to restless leg syndrome.

Chapter 13

Oncology

Q. What are tumour markers? Explain with the help of examples.

- A tumour marker is a biochemical substance elaborated by a particular type of malignancy.
- These markers can be normal endogenous products that are produced at a greater rate in cancer cells or products of newly switched on genes that remained quiescent in the normal cells.
- Can be present in blood, urine or other body fluids, and in tumours and other tissues.
- Assays of such markers may be of great help in a number of ways: (1) Screening of high-risk individuals for the presence of malignancy. (2) Diagnosis of malignancy. (3) Monitoring effectiveness of therapy and regression of tumour. (4) Early detection of recurrence. (5) Immunodetection of metastatic sites.
- Successful use of chemotherapy is associated with disappearance of the abnormal tumour marker.
- Unfortunately, none of the available markers are completely specific for a malignancy. They may be elevated in some benign diseases as well.

Examples

- Beta-human chorionic gonadotropin (β-HCG) is raised in germ cell tumours of testes and ovaries, and trophoblastic tumours.
- Carcinoembryonic antigen (CEA) is raised in bowel malignancies and neoplasms of stomach, pancreas, lung and breast. May also be elevated in cigarette smoking, peptic ulcer disease, inflammatory bowel disease, pancreatitis, hypothyroidism, cirrhosis and biliary obstruction.
- α-foetoprotein (AFP) is raised in hepatocellular carcinoma (HCC) and germ cell tumour of testes.
- Philadelphia (Ph[1]) chromosome is a marker for chronic myelogenous leukaemia (CML).
- Beta-2 microglobulin blood levels are high in multiple myeloma, chronic lymphocytic leukaemia and some lymphomas. Levels may also be higher in kidney disease and hepatitis.
- Prostatic specific antigen (PSA) and prostate acid phosphatase are elevated in prostatic cancer. Other conditions where PSA is elevated include prostatitis, benign prostatic hypertrophy, prostatic trauma and after ejaculation.
- Calcitonin is a marker for medullary thyroid carcinoma.
- Chromogranin A is elevated in neuroendocrine tumours which include carcinoid tumours, neuroblastoma and small cell lung cancer. Use of proton-pump inhibitors also increases its level.
- Hormones are produced ectopically by tumours such as in paraneoplastic syndromes.
- Tumour-associated antigens like cancer antigen 125 (CA-125), CA-19-9, CA-15-3, etc. CA-125 is elevated in ovarian adenocarcinoma. May also be elevated in some patients with malignancies of breast, colon, stomach, oesophagus, biliary tract, pancreas, lung and endometrium. Also elevated in some patients with tuberculosis and benign ovarian tumours, and ascites and pleural effusion. CA-19-9 is high in pancreatic cancers. It may also be elevated in bladder and stomach cancers.
- Oestrogen receptor (ER), progesterone receptor (PR) and HER2 protein in breast cancer patients help in identifying patients likely to respond to hormonal therapies or targeted therapy like trastuzumab.

Q. Discuss α-foetoprotein briefly.

- This oncofoetal antigen is produced by the liver and gastrointestinal tract epithelium during gestation. The α-foetoprotein (AFP) gene is almost completely repressed in fully matured foetus leading to its disappearance soon after birth.
- Although abundant in foetal blood, its concentration is below 15 ng/ml after birth.
- In the prenatal period, amniotic fluid AFP is elevated in open spina bifida, anencephaly and atresia of oesophagus.
- The serum levels are elevated in:
  - 70% of patients with HCC where very high levels ranging between 500 ng/mL and 5 mg/mL are noted.
  - Non-seminomatous testicular cancer (e.g. embryonal carcinoma, teratomas, choriocarcinoma and yolk sac carcinoma), germ cell tumours of ovaries and extragonadal germ cell tumours.
  - Neoplasms of gastrointestinal tract.
- Minimally elevated levels of AFP may be seen in patients with acute or chronic hepatitis.
- AFP is also elevated up to 500 ng/mL in maternal serum during normal pregnancy.
- HCC patients with a high AFP concentration (≥400 ng/mL) tend to have greater tumour size, bilobar involvement, portal vein thrombosis and a lower median survival rate.

Q. Discuss briefly the classification of chemotherapeutic agents.

Class/agents

(A) Alkylating agents
- Busulfan
- Carboplatin
- Carmustine
- Chlorambucil
- Cisplatin
- Cyclophosphamide
- Dacarbazine
- Ifosfamide
- Lomustine
- Mechlorethamine
- Melphalan
- Temozolomide
- Thiotepa

(B) Antitumour antibiotics
- Anthracyclines
  - Daunorubicin
  - Doxorubicin
  - Epirubicin
  - Idarubicin
  - Mitoxantrone
- Bleomycin
- Dactinomycin
- Mitomycin-C
- Plicamycin

(C) Natural products
- Vinca alkaloids
  - Vinblastine
  - Vincristine
  - Vinorelbine
- Taxanes
  - Docetaxel
  - Paclitaxel
- Topoisomerase II inhibitors
  - Etoposide
  - Teniposide
- Topoisomerase I inhibitors
  - Irinotecan
  - Topotecan

(D) Antimetabolites
- Folic acid analogues
  - Methotrexate
- Nucleoside analogues
  - Gemcitabine
- Purine analogues
  - Capecitabine
  - Cladribine
  - Fludarabine
  - 6-Mercaptopurine
  - Pentostatin
  - Thioguanine
- Pyrimidine analogues
  - Azacytidine
  - Cytarabine
  - 5-Fluorouracil
- Substituted urea
  - Hydroxyurea

(E) Hormones/hormone modifiers
- Adrenocorticoids
  - Glucocorticoids
- Androgens
  - Fluoxymesterone
- Antiandrogens
  - Flutamide
  - Nilutamide
- Antioestrogens
  - Tamoxifen
- Aromatase inhibitor
  - Anastrozole
  - Letrozole
- Oestrogens
  - Diethylstilbestrol
- Progestins
  - Megestrol acetate
  - Medroxyprogesterone
- Luteinizing hormone-releasing hormone analogues
  - Goserelin
  - Leuprolide

(F) Biologic response modifiers
- Cytokines
  - Interferon
  - Interleukin
- Retinoid
  - Tretinoin
- Monoclonal antibody
  - Alemtuzumab
  - Rituximab
  - Tositumomab
  - Trastuzumab
- Tyrosine kinase inhibitors
  - Imatinib mesylate
  - Dasatinib
  - Erlotinib
  - Gefitinib
  - Lapatinib
  - Sorafenib
  - Sunitinib
  - Vandetanib

(G) Miscellaneous agents
- Bisphosphonates
  - Pamidronate
  - Zoledronic acid
- Enzymes
  - L-asparaginase
  - Procarbazine
- Others
  - Bortezomib
  - Arsenic trioxide
  - Thalidomide
  - Lenalidomide

- Alkylating agents.
  - Cell-cycle phase-nonspecific agents that substitute an alkyl group for a hydrogen atom; results in cross-linking of DNA strands, and interference with replication of DNA and transcription of RNA.
- Antitumour antibiotics.
  - Inhibit cell division by binding to DNA; interfere with RNA transcription.
- Antimetabolites.
  - Interfere with nucleic acid synthesis by substituting drug for purines or pyrimidines necessary for normal cellular function.
- Hormones/hormone modifiers.
  - Alter cellular metabolism by changing body hormonal milieu for unfavourable tumour growth.
- Natural products.
  - Inhibit mitotic spindle formation and block mitosis.
- Miscellaneous agents.
  - Act by a variety of mechanisms.
- Biologic response modifiers.
  - Modify host's response to tumours.

Q. What do you understand by adjuvant and neoadjuvant chemotherapy?

Adjuvant Chemotherapy

- After surgical removal of a malignancy or after radiotherapy, there may still be some malignant cells left behind.
- When chemotherapeutic drugs are used to kill those remaining malignant cells, it is called adjuvant chemotherapy.

Neoadjuvant Chemotherapy

- It indicates use of chemotherapy before principal treatment using surgery or radiotherapy.
- Administering chemotherapy first can shrink a large malignant tumour, making it easier to remove with surgery or allowing it to be treated more easily with radiation.

Q. Write a brief note on cyclophosphamide.

- This is a nucleophilic alkylating agent that inhibits the DNA synthesis.
- Uses:
  - Autoimmune disorders like SLE, rheumatoid arthritis, Wegener's granulomatosis, PAN and other systemic vasculitis.
  - Lymphomas.
  - Leukaemias.
- Toxicity.
  - Alopecia.
  - Bone marrow depression resulting in thrombocytopenia.
  - Hepatotoxicity.
  - Cystitis and bladder carcinoma. Incidence of cystitis can be reduced by adequate hydration.
  - Severe cystitis can be treated by mercaptoethane sulphonate (MESNA). It can also be used to prevent the occurrence of cystitis.

Q. Give a brief account of uses and toxicity of methotrexate.

- This is a folic acid antagonist, which functions as an antimetabolite. Here, there is competitive inhibition of folate reductase enzyme, and therefore, it inhibits DNA synthesis and consequently cell replication.
- Uses:
  - Choriocarcinoma.
  - Leukaemias.
  - Rheumatoid arthritis and other connective tissue disorders.
  - Psoriasis.
- Toxicity
  - Hepatotoxicity
  - Bone marrow suppression
  - Megaloblastic anaemia

- Ulcerative enteritis, ulcerative dermatitis
- Pulmonary fibrosis.
- Folinic acid (citrovorum factor) is used to antagonise the toxicity of methotrexate.

Q. Describe cisplatin.

- A platinum-based chemotherapy drug (others being carboplatin and oxaliplatin) that produces cross-linking of DNA thereby preventing division of cells.
- The *cis* isomer is cytotoxic to the tumour cells whereas the *trans* isomer does not have an anticancer effect but is more toxic.
- Uses
    - Sarcomas
    - Small cell cancer of lung
    - Ovarian carcinoma
    - Lymphoma
    - Germ cell tumours
    - Bladder carcinoma
    - Breast carcinoma.
- Toxicity
    - Nausea and vomiting
    - Nephrotoxicity
    - Neurotoxicity
    - Ototoxicity
    - Alopecia
    - Electrolyte disturbances (hypomagnesaemia, hypokalaemia and hypocalcaemia)
    - Bone marrow suppression.

Q. What is meant by targeted therapy in cancer patients? Explain the various types of targeted therapies.

- Conventional chemotherapy, although directed towards certain macromolecules or enzymes, typically does not discriminate effectively between rapidly dividing normal cells (e.g. bone marrow and gastrointestinal tract) and tumour cells. This leads to partial response and several side effects.
- Targeted therapy interferes with molecular targets that have a role in tumour growth or progression.
- These targets are usually located in tumour cells. Some targeted agents may target other cells that may affect the tumour cells; e.g. antiangiogenic agents may target endothelial cells.
- Targeted therapies therefore have a high specificity toward tumour cells, providing a broader therapeutic window with less toxicity.
- These agents are often used in combination with cytotoxic chemotherapy or radiation to produce additive or synergistic activity.

Common Types of Targeted Therapies

- Monoclonal antibodies.
- Inhibitors of tyrosine kinases (receptor or non-receptor kinases).
- Inhibitors of proteasomes.
- Immunotoxins.
- Inhibitors of growth factor receptors.

Monoclonal Antibodies

Monoclonal Antibodies Alone

- Rituximab is a chimeric monoclonal immunoglobulin G_1 antibody targeted against the cell surface receptor CD20 common in many B-cell NHL subtypes.
- Produces apoptosis, antibody-dependent cell cytotoxicity and complement-mediated cytotoxicity. Used for relapsed or refractory B-cell non-Hodgkin's lymphoma.
- Patients with malignant cells resistant to apoptosis and patients whose immune systems will not perform antibody- or complement-dependent cytotoxicity may be resistant.

Radioimmunotherapy

- A strategy to optimize the efficacy of anti-CD20 monoclonal antibody therapy as it is not dependent on the mechanism cited above for killing the cells.
- Prepared by combining the antibody with a radioconjugate, yttrium-90 or iodine-131 (e.g. tositumomab combined with iodine-131).
- However, radioimmunotherapy is limited by the potency of the radionuclide and the small number of radionuclide molecules that can be added to each monoclonal antibody molecule. Patients often develop incur dose-limiting toxicity to the bone marrow because of non-specific uptake of antibodies and have an incomplete response.

Conjugate of Monoclonal Antibody

- This involves conjugating chemotherapy molecules to monoclonal antibodies.
- Examples include gemtuzumab ozogamicin, a conjugate of an anti-CD33 monoclonal antibody and calicheamicin, which is approved for acute myelogenous leukaemia.

Tyrosine Kinases and their Inhibitors

- Tyrosine kinases are activated by either growth factors or mutation of genes.
- Activated forms of tyrosine kinases can produce several effects:
    - Increase in tumour cell proliferation and growth.
    - Antiapoptotic effects.
    - Promote angiogenesis and metastasis.

Non-Receptor Tyrosine Kinase Inhibitors

- Imatinib inhibits non-receptor tyrosine kinase BCR–ABL.
- Useful in several haematological malignancies particularly chronic myeloid leukaemia.

Receptor Tyrosine Kinase Inhibitors

- These target epidermal growth factor receptors (EGFR), vascular endothelial growth factor receptors (VEGFR) and platelet-derived growth factor receptors (PDGFR).
    - Gefitinib, erlotinib and lapatinib act on EGFR.
    - Vatalanib and semaxanib target VEGFR.
    - Leflunomide targets PDGFR.

Proteasome Inhibitors

- Proteasome is an organelle responsible for the physiologic degradation and recycling of cellular proteins that regulate cell cycle progression.
- A variety of cancer cells are more sensitive than normal cells to inhibition of proteasomes.
- Bortezomib, a proteasome inhibitor is useful for the treatment of relapsed/refractory multiple myeloma patients.

Immunotoxins

- Contain a toxin along with an antibody or growth factor that binds specifically to target cells.
- Immunotoxin binds to the target cell, internalized and then the enzymatic fragment of the toxin kills the cell by inhibiting protein synthesis.
- Various plant and bacterial toxins can be used but the one in clinical use is human interleukin-2 combined with truncated diphtheria toxin that is approved for use in cutaneous T-cell lymphoma.

Q. Write a brief note on the role of positron emission tomography in oncology.

- In oncology, positron emission tomography (PET) is used for screening, for preliminary diagnosis, to establish the extent and distribution of disease, for biopsy guidance, staging, prognostication, therapeutic planning and judging response to therapy.
- PET provides information about the functional and metabolic changes associated with cancer.
- PET scanning requires use of molecules that are labelled with radionuclides. In clinical practice, the principal radioisotope used is the positron emitting 18F-fluorodeoxyglucose (18F-FDG), which is a glucose analogue labelled with 18F. It has a short half-life and is produced in cyclotrons.
    - FDG is injected intravenously and is transported from the plasma to the cells by glucose transporters (GLUT 1 and GLUT 4).

- It then undergoes phosphorylation within the cell by the enzyme hexokinase and is converted to FDG-6-phosphate.
  - FDG-6-phosphate is not further metabolised and gets trapped in the cell.
- Cancer cells demonstrate increased anaerobic glycolysis and reduced levels of glucose-6-phosphatase thus, limiting further metabolism of the tracer in cancer cells.
- PET–CT combines the functional information from a PET scan with the anatomical information from a CT scan. It can pinpoint the exact location of abnormal activity.
- PET has been found to be useful in several malignancies including melanoma, lymphoma, lung cancer, oesophageal cancer, head and neck cancer, breast cancer and thyroid cancer.
- FDG uptake may occur in various types of active inflammation and infections and is not specific for cancer. Thus it is not used for the initial diagnosis of cancer, but is useful in monitoring cancer cell viability and for the diagnosis and detection of recurrence of cancer. PET is also useful for monitoring the response to treatment of various cancers.
- PET is also useful in diagnosing certain cardiovascular and neurological diseases because it highlights areas with increased, diminished or no metabolic activity.
- PET is also positive in patients with granulomatous diseases like tuberculosis and sarcoidosis.

False Negative Results

- Tumours with slow growth and with low metabolism, e.g. some cases of bronchioloalveolar cell carcinomas, well differentiated adenocarcinomas, and carcinoid tumours.
- Small tumours less than 7 mm in diameter may not be detected
- Hyperglycaemia decreases intracellular FDG uptake because the FDG and glucose compete for the same cell surface receptor.

Q. Enumerate emergency conditions related to tumours.

Q. Describe febrile neutropenia.

Q. Write briefly on the clinical features and treatment of lysis syndrome.

Oncologic Emergencies

Metabolic	**Anatomical**
- Tumour lysis syndrome	- Superior vena cava syndrome
- Hypercalcaemia	- Epidural spinal cord compression
- Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	- Cardiac tamponade
Haematologic	
- Febrile neutropenia	
- Thrombocytopenia	
- Hyperviscosity syndrome	
- Disseminated intravascular coagulation	

Febrile Neutropenia

- A major complication of cancer chemotherapy.
- Defined as an oral temperature >38.5°C or two consecutive readings of >38.0°C for 2 hours and an absolute neutrophil count <500/mm³ or <1,000/mm³ with predicted decline to less than 500/mm³ within the next 2 days.

Management

- An initial assessment of circulatory and respiratory function with vigorous resuscitation.
- Careful examination for potential foci of infection.
- Signs and symptoms of infection in neutropenic patients can be minimal particularly in those receiving corticosteroids.
- Before antibiotic therapy, send two sets of blood cultures from a peripheral vein and any indwelling venous catheters. In addition, sample sputum, urine, skin swabs and stool specimens if clinically indicated.
- Intravenous broad-spectrum antibiotics (e.g. ceftazidime, meropenem or imipenem, piperacillin/tazobactam) with or without an aminoglycoside.
- Gram-positive coverage should be added in patients with any of the following findings: haemodynamic instability, pneumonia, positive blood cultures for gram-positive bacteria while awaiting susceptibility results, suspected central

venous catheter-related infection, skin or soft tissue infection and severe mucositis in patients who were receiving prophylaxis with a fluoroquinolone.
- Granulocyte-colony stimulating factor (G-CSF) may be given in patients with pneumonia, hypotension, organ dysfunction or a patient on a regimen that is known to cause prolonged neutropenia. However, efficacy is modest.
- In some low-risk patients (haemodynamically stable, who do not have acute leukaemia or evidence of organ failure, who do not have pneumonia, an indwelling central venous catheter or severe soft tissue infection), oral antibiotics (combination of quinolone and amoxicillin/clavulanate) may be given.

Prevention

- Prophylactic fluoroquinolones for high-risk and intermediate-risk groups, which largely comprise patients receiving high-dose chemotherapy and those with haematological malignancy in which the anticipated duration of neutropenia is longer than 7 days.
- For most solid tumours undergoing standard outpatient cyclical chemotherapy in which the anticipated duration of neutropenia is less than 7 days, prophylactic fluoroquinolones are not recommended because of the risk of microbial resistance.
- G-CSF may be used prophylactically in patients with some types of malignancies receiving chemotherapy where risk of neutropenia is greater than 20%.

Tumour Lysis Syndrome

- Occurs 1–5 days post-chemotherapy and is due to rapid release of intracellular contents and nucleic acids.
- The syndrome is most common in lymphoma and leukaemia.
- Spontaneous lysis in the absence of treatment may occur in rapidly proliferating tumours, especially Burkitt lymphoma, large T-cell lymphoma and acute lymphocytic leukaemia.
- Risk factors include large tumour burden, high growth fraction, increased pretreatment LDH or uric acid, or preexisting renal insufficiency.

Clinical Features

- Lysis of malignant cells causes several metabolic disturbances. Hyperuricaemia produces acute renal failure; hyperkalaemia leads to cardiac arrhythmias; hyperphosphataemia produces acute renal failure and hyperkalaemia; and hypocalcaemia results in seizures, muscle cramps, tetany and arrhythmia.

Treatment

- It is important to prevent this syndrome by adequate hydration and diuresis before, during and after the treatment.
- Pretreatment with allopurinol blocks conversion of hypoxanthine and xanthine to uric acid.
- Rasburicase is a recombinant urate oxidase that converts uric acid into an inactive and soluble metabolite, allantoin that is easily excreted by the kidneys. Because hydrogen peroxide is a byproduct of uric acid catabolism to allantoin, rasburicase can cause haemolytic anaemia or methaemoglobinaemia in patients with glucose-6-phosphate dehydrogenase deficiency.
- Alkalinization of urine to promote uric acid excretion is controversial as it may worsen hypocalcaemic tetany. It may also increase the risk of nephropathy due to xanthine and calcium phosphate crystal precipitation.
- Manage life-threatening hyperkalaemia with antihyperkalaemic measures.
- For hypocalcaemia, infuse calcium gluconate under ECG monitoring.
- Early dialysis is required if uric acid >10mg/dL, phosphorus >10mg/dL or creatinine >10mg/dL.

Q. What are proto-oncogene, oncogene and tumour suppression genes?

Q. Describe the genetic basis of transformation of a normal cell into a malignant cell.

- Cancers arise from uncontrolled cellular proliferation caused by activation and inactivation of certain genes that are normally present in the cells. These genes are called proto-oncogenes and tumour suppression genes respectively.

Proto-Oncogenes and Oncogenes

- The non-activated genes are proto-oncogenes that usually promote normal cell growth. Their activation to oncogenes is responsible for the development of cancers. Activation of proto-oncogenes to oncogenes can occur in the following ways.

Mutations

- Carcinogens, ionizing radiation and ultraviolet light can cause point mutation in the proto-oncogenes that in some cases can activate them to oncogenes. Not all mutations in a proto-oncogene cause cancers.

Chromosomal Translocation

- If during a cell division two chromosomes translocate (i.e. part of one chromosome attaches to the other), it is possible that part of a proto-oncogene gets translocated to another chromosome and fuses with the gene present on that chromosome. This may result in inappropriate expression of the gene.
- An example is the development of Philadelphia chromosome in patients with chronic myeloid leukaemia. This chromosome arises from a translocation between the long arms of chromosomes 9 and 22. Consequently, the ABL gene on chromosome 9 gets joined to the *BCR* gene on chromosome 22. The resultant fused gene is thought to cause the leukaemic transformation.

Viral Stimulation

- The viral DNA may integrate within a proto-oncogene resulting in its transformation.
- Alternatively, the virus may incorporate the proto-oncogene into its genome, and later when this virus infects another person this oncogene is transferred to the new host. For example, the Rous sarcoma virus of chickens was found to induce cancers because it carried the *ras* oncogene.

Tumour Suppressor Genes

- These genes restrict the abnormal proliferation of cells and induce repair or self-death (apoptosis).
- Mutations of these genes may cause abnormal proliferation of cells and development of cancers. Mutation of both the genes (present on a pair of chromosome) is required for their inactivation.
- The first tumour suppressor gene described was *RB* gene. Mutation in this gene may produce retinoblastoma.
- Other important tumour suppressor genes are *p53*, *BRCA1* and *BRCA2*. As many as 50% of human tumours have mutated *p53* gene. *BRAC1* and *BRAC2* are seen in breast and ovarian malignancies.

Q. Describe apoptosis.

- Necrotic cell death occurs when external factors (e.g. hypoxia, toxins, etc.) produce disintegration of cells. Characteristically, there is an influx of water and ions that results in swelling and rupture of cellular organelles. Lysis of cells releases lysosomal enzymes and other mediators that induce acute inflammatory responses.
- In apoptosis, physiological cell death occurs through activation of genes. The features of apoptosis are:
  - Chromatin aggregation with nuclear and cytoplasmic condensation into distinct membrane-bound vesicles (apoptotic bodies). Organelles remain intact.
  - Cell "blebs" (intact membrane vesicles) on the surface. No inflammatory response.
  - Phagocytosis by surrounding cells and macrophages.
- Apoptosis is essential part of life. It plays a role in tissue formation during embryogenesis, wound healing, metabolic processes and control of abnormal cells with oncogenic potential. This phenomenon is also essential for effects of chemotherapy and radiotherapy in cancer patients.

Chapter 14
Genetics and Diseases

Q. Write a short note on chromosomes.

- Present in the nucleus of cells.
- Made up of double-stranded, helical deoxyribonucleic acid (DNA).
- The DNA molecule is complexed with histones and non-histone proteins to form a deoxyribonucleoprotein fibre called chromatin. Chromatin is the basic unit of a chromosome structure.
- DNA is made up of nucleic acids that are composed of molecules of nucleotides.
- Each nucleotide has three components:
  - Nitrogenous bases
    - Purines—adenine (A) and guanine (G)
    - Pyrimidines—cytosine (C) and thymine (T)
  - Sugar moiety—deoxyribose
  - Phosphate molecules.
- Adenine pairs with thymine and cytosine with guanine to form a base pair.
- A sequence of three bases forms a codon that codes for an amino acid.
- Each chromosome consists of a single, enormously long and linear DNA molecule associated with proteins that fold and pack DNA into a more compact structure. The complex of DNA and protein is called chromatin.
- Human somatic cell contains a set of 46 chromosomes. Two of these chromosomes determine the sex of the individuals, i.e. sex chromosomes (X and Y). The remaining 44 chromosomes are known as autosomes. The two sex chromosomes of the female are X chromosomes (XX). Y chromosome is morphologically smaller than X chromosome. Male sex is determined by XY chromosomes.
- With the exception of germ cells (sperm and eggs) and highly specialised cells that lack DNA entirely (such as red blood cell), each human cell contains two copies of each chromosome, one inherited from the mother and one from the father; the maternal and paternal chromosomes of a pair are called homologous chromosomes. The only non-homologous chromosome pairs are the sex chromosomes in males, where a Y chromosome is inherited from the father and an X chromosome from the mother.
- Arrangement of chromosomes in pairs in decreasing order of size is known as karyotype of chromosomes and is numbered 1–22. The 23rd pair is the sex determining (X and Y) chromosomes.
- A karyotype is obtained from peripheral blood lymphocytes using various stains. A more rapid method is by fluorescence in situ hybridisation (FISH).
- Each chromosome has a short arm known as "p" arm and a long arm known as "q" arm.
- Since there are 46 chromosomes in a normal individual, males have 46 XY chromosomal pattern while females have 46XX.
- Deletion or addition of a chromosome is shown as a "+" or "−" sign. For example, Down's syndrome has one extra-autosomal chromosome and a male is represented as 47 XY, +21 (indicating one extra chromosome number 21).
- If a part of one arm is missing, it is indicated as 46 XY, 5p− (indicating deletion of short arm of chromosome number 5 as occurs in Cri-du-chat syndrome).
- Mitochondria have a distinct genome consisting of 16,589 base pairs. The mitochondrial genome encodes 37 genes, including 13 proteins. Mitochondria are transmitted only in the ovum and as such, all mitochondrial DNA is maternally inherited.

Q. Describe human genome.

Q. Give a brief account of human genome project.

- A genome is an organism's complete set of DNA, including all of its genes. Each genome contains all the information needed to build and maintain that organism.
- The human genome is the genome of *Homo sapiens*, which is composed of 46 distinct chromosomes (22 pairs of autosomal chromosomes + XX or XY chromosomes).
- The Human Genome Project (HGP) is an international effort, which began in 1990. The project was planned to last 15 years, but rapid technological advances have accelerated the completion to 2003.
- Its main aim was to decode a total of approximately 3 billion DNA base pairs containing estimated 20,000–25,000 genes.
- It has produced a reference sequence of the human genome which is used worldwide in biomedical sciences.

- The human genome is much more gene-sparse than was initially predicted at the outset of the HGP, with only about 1.5% of the total length serving as protein-coding exons, and the rest of the genome comprised by introns or so-called junk DNA.
- All humans have unique gene sequences, therefore the data published by the HGP does not represent the exact sequence of each and every individual's genome. It is the combined genome of a small number of anonymous donors.
- 99.9% of information in the estimated 20,000 human genes is identical from one person to the next. The small differences in the remaining 0.1% of genes present in the human cells are the key to each individual.

Potential Benefits of Human Genome Project

- Molecular medicine.
  - Improved diagnosis of disease.
  - Earlier detection of genetic predispositions to disease.
  - Gene therapy.
  - Pharmacogenomics ("custom drugs" to target specific genetic composition so as to get best drug response with minimal side effects).
- Energy and environmental applications.
  - Use microbial genomics research to create new energy sources (biofuels).
  - Use microbial genomics research to develop environmental monitoring techniques to detect pollutants.
- Risk assessment.
  - Assess health damage caused by radiation exposure.
  - Assess health damage caused by exposure to mutagenic chemicals and cancer-causing toxins.
- DNA forensics (identification).
  - Identify potential suspects, whose DNA may match evidence left at crime scenes.
  - Exonerate persons wrongly accused of crimes.
  - Establish paternity and other family relationships.
  - Match organ donors with recipients in transplant programs.

Ethical, Legal and Social Issues of Human Genome

- Privacy and fairness in the use of genetic information, includes the potential for genetic discrimination in employment and insurance.
- Integration of new genetic technologies (e.g. genetic testing) into the practice of clinical medicine.
- Ethical issues surrounding the design and conduct of genetic research in people.
- Education of healthcare professionals, policy makers, students and public about genetics and the complex issues that result from genomic research.

Q. Give a brief account on proteomics.

Q. Describe proteome.

- Study of the full set of proteins in a cell type or tissue and the changes during various conditions, is called proteomics.
- The word "proteome" is derived from proteins expressed by a genome, and it refers to all the proteins produced by an organism, much like the genome is the entire set of genes. The human body may contain more than 2 million different proteins, each having different functions.
- Study of proteomics is important, since proteins and the genomes are the functioning units.
- However, the task of studying the proteome involves the sheer number of proteins that need to be identified. Another challenge is that amino acids—the base units of proteins—are very small. Each amino acid is made from anywhere between 7 and 24 atoms. This is far beyond the reach of even the most powerful microscopes.
- Proteomic technologies will play an important role in drug discovery, diagnostics and molecular medicine because of the link between genes, proteins and disease. As more and more defective proteins causing particular diseases are found, new drugs will be developed to either alter the shape of a defective protein or mimic a missing one.

Q. Explain pharmacogenetics.

Q. Describe pharmacogenomics.

- Study of interaction between genetics and therapeutic drugs is variously called pharmacogenetics or pharmacogenomics. Differences between the two are the initial approach of the science:
  - Pharmacogenetics starts with an unexpected drug response result and looks for a genetic cause.

- Pharmacogenomics, on the other hand, begins with looking for genetic differences within a population that explain certain observed responses to a drug or susceptibility to a health problem.
- Potential applications include:
  - Development of drugs that maximise therapeutic effects but decrease damage to adjacent healthy cells.
  - Prescription of drugs based on the patient's genetic profile so as to decrease likelihood of adverse reactions.
  - More accurate methods of determining dosages.
  - Determine drug responses in the treatment of cardiac, respiratory and psychiatric conditions.
  - Develop targeted drugs in areas such as psychiatry, dementia, cardiac conditions, and in the treatment of breast and other cancers (e.g. testing for HER2 receptor in breast cancer for response to trastuzumab; BCR–ABL testing for response to imatinib in CML; epidermal growth factor receptor testing for response to gefitinib and erlotinib in lung cancer).

Q. Write a short note on epigenetics.

- It is a study of transmission of information from a cell or multicellular organism to its descendants without that information being encoded in the nucleotide sequence of the gene.
- This term is used to refer to features such as chromatin and DNA modifications that are stable over rounds of cell division but do not involve changes in the underlying DNA sequence of the organism. In other words, epigenetics refers to variability in gene expression, heritable through mitosis and potentially meiosis without any underlying modification in the actual genetic sequence.
- These epigenetic changes play a role in the process of cellular differentiation, allowing cells to stably maintain different characteristics despite containing the same genomic material.
- Epigenetic features are inherited when cells divide despite a lack of change in the DNA sequence itself, and although most of these features are considered dynamic over the course of development in multicellular organisms, some epigenetic features show trans-generational inheritance and are inherited from one generation to the next.
- Potential clinical applications include:
  - Epigenetic tumour markers.
  - Epigenetic therapeutic agents (e.g. azacitidine, decitabine, vorinostat) that are used in the treatment of myelodysplastic syndromes and progressive lymphoma.

Q. Discuss the various types of chromosomal aberrations.

- Chromosomal aberrations may be summarised as follows:
  - Autosomal abnormalities.
  - Sex-linked abnormalities.
- Both autosomal and sex-linked abnormalities may be due to:
  - Numerical abnormalities (number of chromosomes different from normal).
  - Structural abnormalities (change in structure of a chromosome due to addition or deletion of a part of it).

Numerical Abnormalities of Autosomal Chromosomes

- Polyploidy—One whole set of chromosomes (i.e. 23 chromosomes) is gained (3n, 4n; normal pattern is 2n). This is not compatible with life.
- Aneuploidy—One or more chromosomes are either gained or lost.
  - Monosomy—Loss of one chromosome (instead of the typical two in humans) from a pair of autosomes ($2n - 1$). This is lethal in males.
  - Trisomy—Addition of an extra autosome chromosome ($2n + 1$). e.g.
    - (i) Down's syndrome (trisomy-21; 47 XY, +21).
    - (ii) Patau's syndrome (trisomy-13; 47 XY, +13).
    - (iii) Edwards' syndrome (trisomy-18; 47 XY, +18).

Numerical Abnormalities of Sex Chromosomes

- More common than numerical abnormalities of autosomal chromosomes (except Down's syndrome).
- Occurs due to failure of homologous chromosomes to separate in one of the cycles of meiosis during spermatogenesis or oogenesis. This is known as non-disjunction.
- Monosomy is seen with Turner's syndrome (45 X or 45 X0).
- Presence of more than one X chromosomes produces higher risk of mental retardation (e.g. Klinefelter's syndrome—47 XXY).
- Presence of more than one Y chromosome (e.g. 47 XYY) results in tall males with aggressive behaviour.

Structural Abnormalities of Chromosomes

- Deletion—loss of part of a chromosome (e.g. loss of short arm of chromosome number 5 produces Cri-du-chat syndrome; 46 XY, 5p−).
- Translocation—exchange of segments between two non-homologous chromosomes, i.e. recombination of two unrelated genes to form new genetic information (e.g. Down's syndrome in a small proportion of patients due to translocation of segments of chromosomes 21 and 14; Philadelphia chromosome due to translocation between chromosomes 9 and 22).
- Ring chromosomes—fusion of the two ends of the same chromosome; there is loss of genetic material at the ends of the chromosome prior to the fusion. It is denoted by symbol "r" (e.g. ring chromosome 20 is associated with epilepsy).
- Isochromosomes—a chromosome with two genetically identical arms, i.e. two "p" or two "q" arms (e.g. some cases of Turner's syndrome).

Q. Discuss the genetic basis of human diseases.

Q. Write a short note on unifactorial, multifactorial and chromosomal disorders.

- Gregor Mendel is considered as the father of genetics.
- The mode of inheritance of genetic disorders follows Mendelian principles.
- The spectrum of genetic disorders includes the following three categories:
  - Unifactorial disorders or monogenic disorders
    - These disorders are due to single-mutant gene defects.
    Note: Several of these diseases are now known to be due to different mutations in the same gene or mutations involving closely associated genes. Degree of severity and time of onset are controlled by mutations in an unknown number of modifier genes.
  - Multifactorial disorders
    - These disorders are caused by an interaction of genetic and environmental factors.
  - Chromosomal disorders
    - These disorders result from an abnormality of number or structure of chromosomes (discussed above).

Unifactorial Disorders
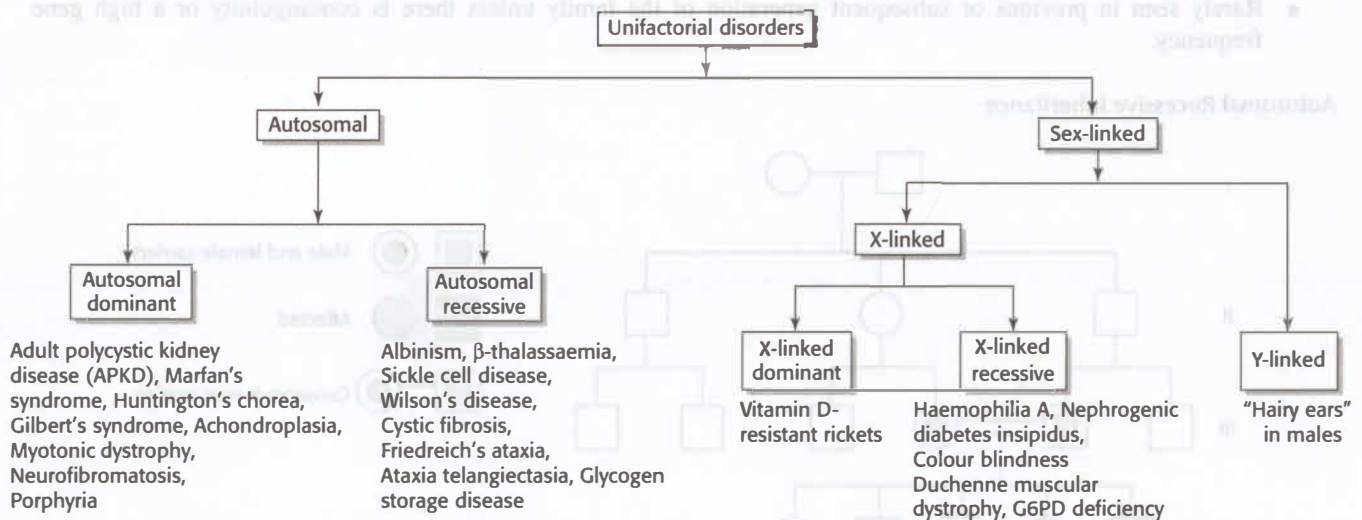
Autosomal Dominant Diseases

- Disorders generally manifest when one of the two homologous (paired) chromosomes carries a mutant gene at the locus involved (allele).
- Characterised by:
  - Vertical transmission to subsequent generations.
  - One parent is affected in most cases.
  - 50% chances that the child of an affected parent will be affected.
  - Males and females are equally affected.

- Some autosomal dominant diseases may show variable expression, i.e. variation in severity of the same disease (autosomal dominance with variable penetrance). Sometimes, the gene is not expressed at all (non-penetrance) that explains apparent skipping of generations.

Autosomal Dominant Inheritance
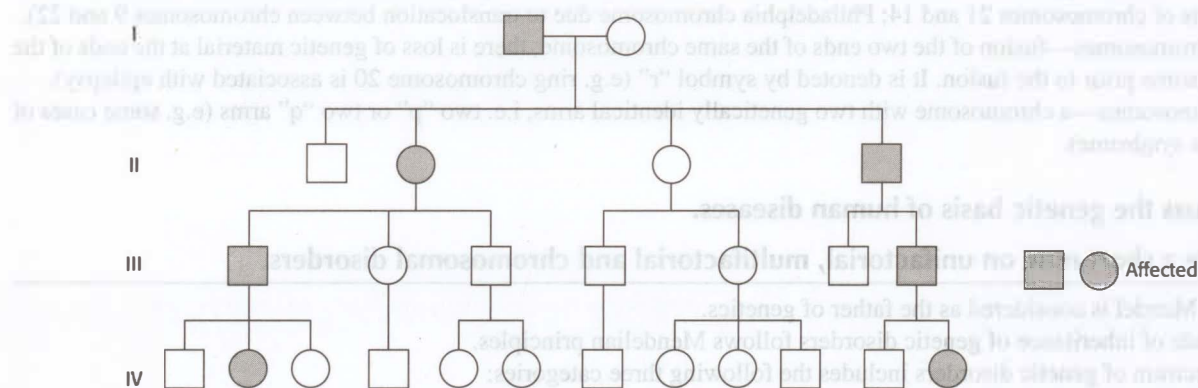
Autosomal Recessive Diseases

- Disorders generally manifest, when both the homologous chromosomes carry mutant genes at the locus involved (homozygous state).
- Disease generally are not manifested when only one mutant allele is present (i.e. in heterozygous state).
- Characterised by:
  - Males and females are equally likely to be affected.
  - Disease not present in parents, offspring or other relatives of affected person (horizontal transmission).
  - Birth of an affected child establishes both parents as carriers of a single copy of the gene mutation.
  - Chance of a second affected child in the sibship is one in four or 25% in each pregnancy. Fifty percent are heterozygotes (clinically normal) and 25% are normal without any mutant gene.
  - Rarely seen in previous or subsequent generation of the family unless there is consanguinity or a high gene frequency.

Autosomal Recessive Inheritance
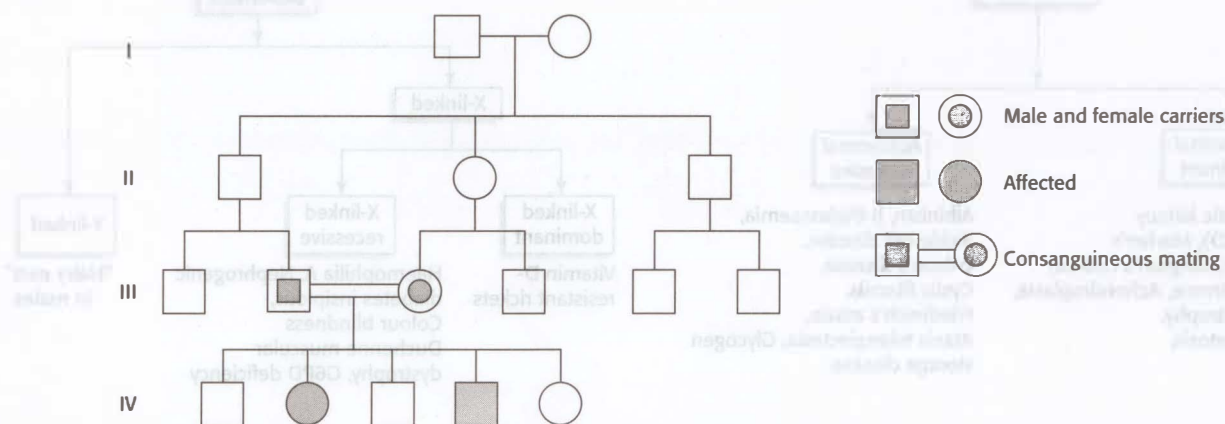
X-Linked Dominant Diseases

- Mutant gene on X chromosome.
- Characterised by:
  - No carriers as the disease will manifest even if single chromosome has abnormal gene.
  - The trait is never passed from father to son as the son's "normal" X chromosome is from mother.
  - All daughters of an affected father are diseased as the daughter gets abnormal X from the father.

- If mother is affected and father is normal, 50% of both sons and daughters are affected.
- In general, males are more severely affected than females. The trait may be lethal in males.

X-Linked Dominant Inheritance
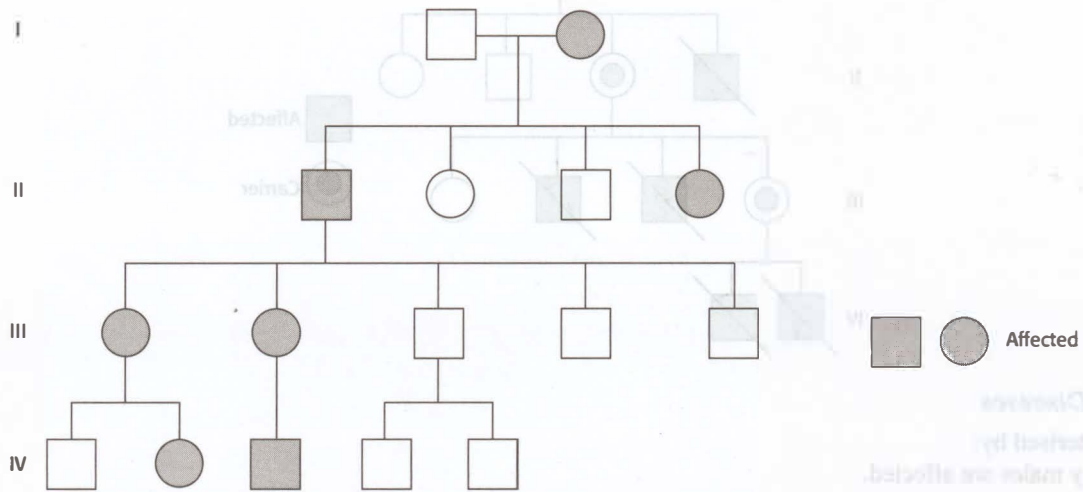
Affected

X-Linked Recessive Diseases

- Mutant gene on X chromosome.
- Characterised by:
  - As with any X-linked trait, the disease is never passed from father to son.
  - Manifests only in males. In many diseases males do not survive.
  - All affected males in a family are related through their mothers.
  - Trait or disease is typically passed from an affected grandfather through his carrier daughters to half of his grandsons.
  - Mothers are always carriers and all their sons are affected.
- Very rarely, a female can develop the disease. This may occur due to:
  - Female also having Turner's syndrome (XO) where only one X chromosome is present.
  - Presence of testicular feminization syndrome.
  - Normal father with mutation in X chromosome and a carrier female.
  - Affected father and carrier mother.
  - Inactivation of normal X chromosome in most cells (Lyon hypothesis).

X-Linked Recessive Inheritance (With Males Surviving To Reproduce)

Affected

Carrier
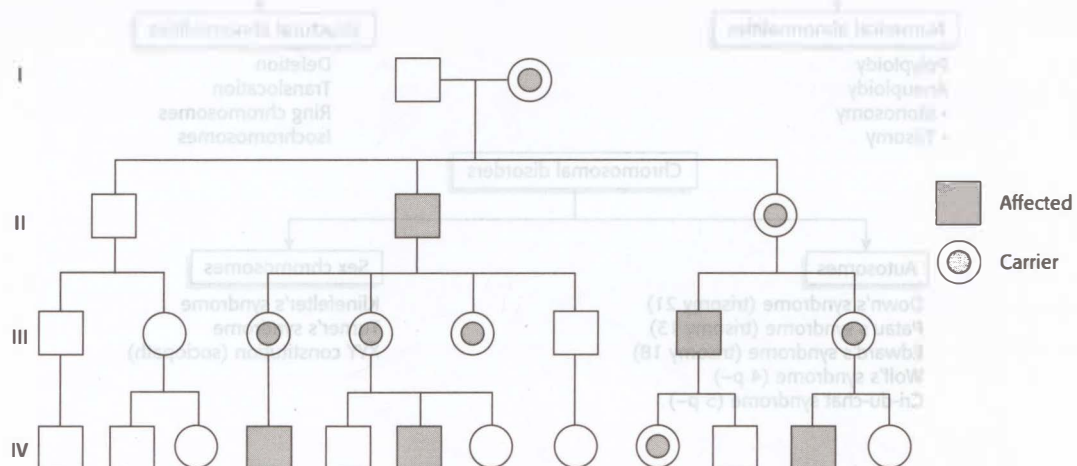
X-Linked Recessive Inheritance (With Males Not Surviving To Reproduce)
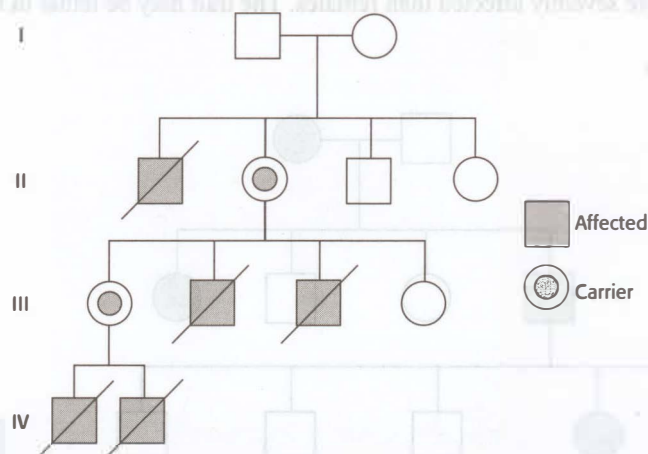
Y-Linked Diseases

- Characterised by:
  - Only males are affected.
  - An affected male transmits the trait to all his sons but not to his daughters.

Multifactorial Disorders
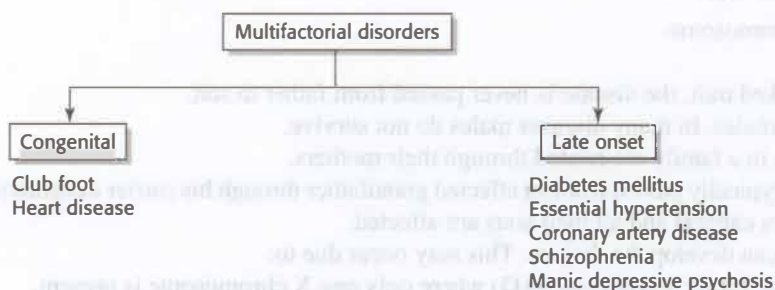
Chromosomal Disorders

- Chromosomal disorders may be classified in two ways:
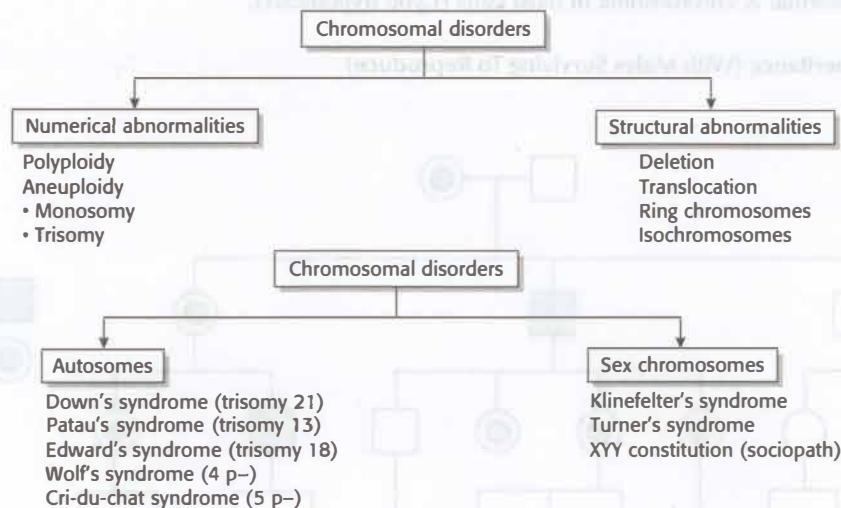
Q. Describe Mongolism (Down's syndrome).

- Autosomal abnormality where the number of the autosomes is affected (autosomal imbalance).
  - Extra chromosome 21 (trisomy 21) due to nondisjunction during meiosis (95%).
  - 1% mosaicism—two different cell lines are present, one has normal chromosomal constitution whereas the other has an extra chromosome 21.
    - 4% due to translocation.
- Incidence—1:700 of live births.
- Significant relationship to increasing maternal age.

Clinical Features

- Typical facies is characterised by flat nasal bridge, mouth hanging open, flat face, widely spaced eyes (hypertelorism) and upward, slanting eyes with epicanthic folds, malformed ears and protruding furrowed tongue (Mongoloid facies). Other features are:
  - Broad, short neck.
  - Brachycephaly.
  - Simian crease—single palmar flexion crease (50% cases).
  - Mental deficiency.
  - An almond shape to the eyes caused by an epicanthic fold of the eyelid.
  - Brushfield's spot on iris.
  - Short stature, hypotonia.
  - Fondness for music.
  - Congenital heart diseases—e.g. ASD, VSD, tetralogy of Fallot and endocardial cushion defects.
  - Increased frequency of leukaemia.
  - Increased risk of sleep apnoea.

Q. Briefly outline the clinical features, diagnosis, complications and management of Klinefelter's syndrome.

- Most common chromosomal disorder.
- Sex chromosomal abnormality.
- Due to nondisjunction of X chromosome during meiosis.
- Males are affected and they have an extra X chromosome.
- Most common karyotype is XXY.
- Other karyotypes include XXXY/XXXXY/XXYY.

Clinical Features

- Sterility (azoospermia), small testes.
- Gynaecomastia.
- Eunuchoid body proportions.
- Sparse facial, body and sexual hair.
- Mental retardation.
- Related to maternal age.

Diagnosis

- Extra X chromosome may be detected as a Barr body on buccal smears. For confirmatory diagnosis, chromosome analysis on lymphocytes from peripheral blood is used.
- For prenatal diagnosis, chromosome analysis on amniocytes or chorionic villi.
- Elevated follicle stimulating hormone (FSH), luteinizing hormone (LH), oestradiol and low to low-normal testosterone level.

Complications

- Risk of acquiring breast carcinoma in 47, XXY is increased with relative risk exceeding 200 times.
- Associated endocrine complications include diabetes mellitus, hypothyroidism and hypoparathyroidism.
- Autoimmune diseases, such as systemic lupus erythematosus, Sjogren's syndrome and rheumatoid arthritis are more common with frequencies similar to those found in females.
- Development of varicose veins and leg ulcers.
- Decreased bone density.

Management

- Testosterone treatment should begin at puberty, around age 12 years, in increasing dosage sufficient to maintain age-appropriate serum concentrations of testosterone, estradiol, FSH and LH. It promotes normalisation of body proportions and development of normal secondary sex characteristics. However, it does not affect infertility, gynaecomastia and small testes. It also reduces long-term complications of osteoporosis, autoimmune disease and breast cancer.
- Early speech therapy.
- Physical therapy for hypotonia or delayed motor skills.

Q. Discuss briefly about Turner's syndrome.

- Sex chromosomal abnormality.
- Due to nondisjunction of X chromosome during meiosis.
- Females are affected where there is a deletion of X chromosome.
- Genetic constitution hence becomes 45 XO.
- In some cases, a combination of monosomy X and normal cells (45,X/46,XX) are present; it is known as mosaic Turner's syndrome.

Clinical Features

- Short stature.
- Webbed neck and low posterior hairline.
- Broad chest—"shield chest".
- Increased carrying angle at the elbows (cubitus valgus).
- Lymphoedema most common reason to screen for Turner's syndrome during infancy.
- Mild mental retardation.
- Infertility.
- Primary amenorrhoea with elevated follicle stimulating hormone (FSH).
- Coarctation of aorta or bicuspid aortic valve.
- Lack of secondary sexual characteristics.
- Not related to maternal age.

Treatment

- Growth hormone increases height in these patients.
- Addition of low dose of oestrogen is also beneficial. It allows for normalised development of secondary sexual characteristics, as well as uterine and bone mineral development.
- Correction of congenital heart diseases.

Q. Explain mental retardation.

- Also known as intellectual disability.
- Here the mental insufficiency is characterised by limitation in adaptive behaviour and intellectual functioning. Various features are:
    - Slowness in motor development.
    - Inability to learn.
    - Poor school progress.
    - Behavioural abnormalities like dull or silly behaviour.
    - Aberrant types of behaviour (autism or hyperkinetism).
    - Dull, apathetic and underactive person.
    - Personality disorders.
    - Social or language disorders.
    - Associated neurologic problems like motor or sensory handicaps, seizures, blindness, deafness, chorea, choreoathetosis, etc.
- Causes
    - Genetic disorders like Down's syndrome and fragile X syndrome.
    - Environmental causes
        - Prenatal exposure to alcohol, lead, mercury, hydantoin, valproate and radiation.
        - Perinatal causes like preterm birth, hypoxia, infection, trauma, intracranial haemorrhage.
    - Hydrocephalus, microcephaly.

- Congenital rubella syndrome, congenital infections.
- Cerebral palsy.
- Post-traumatic, post-meningitic and post-encephalitic states.
- Birth trauma, and kernicterus.
- Metabolic diseases like cretinism, phenylketonuria, mucopolysaccharidoses.
- Degree of mental retardation is assessed by IQ testing (intelligence quotient).

$$IQ = \frac{Mental\ age}{Chronological\ age}$$

Mental Retardation by IQ Range

• Mild	50–55 to ~70
• Moderate	35–40 to 50–55
• Severe	20–25 to 35–40
• Profound	Below 20–25

Q. Discuss the prevention of genetic diseases.

- Premarital career screening.
- Genetic counselling.
- Detection of genetic association—i.e. markers.
  - Restriction fragment length polymorphism (RFLP).
  - Polymerase chain reaction (PCR) techniques.
- Antenatal diagnosis.
  - Amniocentesis.
  - Biochemical, cytogenetic and DNA studies.
  - Transcervical chorionic villous biopsy (chorionic villous sampling—CVS).
- Pre-implantation diagnosis.
  - In vitro fertilisation of the ovum and culture to blastomere stage. One cell is then studied by PCR or gene probe technique to detect genetic markers of diseases.

Q. Give a brief account of gene therapy.

- Genetic disorders are caused when the genes are altered so that the encoded proteins are unable to carry out their normal functions. Similarly, cancers are caused when oncogenes are activated or tumour suppressor genes are inactivated.
- Gene therapy is a technique for correcting defective genes responsible for disease development by using genetic material.
- Besides monogenic disorders, such as cystic fibrosis, haemophilia, muscular dystrophy, sickle cell anaemia, etc. It is also a potential therapy in more complex disorders, such as cardiovascular diseases, diseases of nervous system, autoimmune diseases, congenital immunodeficiency diseases and cancer.

Forms

- Germ-line gene therapy refers to modification of the germ line cells. It is not accepted at present due to ethical reasons.
- Somatic germ therapy refers to genetic modification of different somatic cells. This can be achieved by following ways:
  - Insertion of a normal gene into a non-specific location within the genome to replace a non-functional gene.
  - Repair of defective gene through selective reverse mutation.
  - Swapping an abnormal gene for a normal gene (homologous recombination).
  - Alteration of the regulation of an abnormal gene.
- It can also be a tool for the treatment of non-genetic and polygenic disorders by delivering genes that stimulate immune response, suicidal genes inducing cell death, genes modifying cellular information or developmental programme, or genes producing a therapeutic protein with specific functions.
- In cancers, gene therapy can be in various forms including use of cancer vaccines (immunotherapy), target viruses to cancer cells for lysis and death (oncolysis) and introduce genes into the cancer cells that cause death or restore normal cellular phenotype (gene transfer).
- Gene doping—transfer of cells or genetic elements (e.g. DNA, RNA) or the use of pharmacologic or biologic agents that alter gene expression, with the potential to enhance athletic performance. It is a prohibited method for improving performance.

Approaches

- Two different approaches:
  - In "*ex vivo*" gene therapy, specific cells are isolated and purified from a patient, genetically modified and reinfused.
  - In "*in vivo*" gene therapy, genes are directly transferred into the tissue of patients using a vector. This is most often used technique.
    - A "normal" gene is inserted into the genome to replace the disease-causing gene. A carrier molecule called a vector is used to deliver the therapeutic gene to the patient's target cells. Currently, the most common vector is a virus. Commonly used viruses include retroviruses (e.g. Moloney murine leukaemia virus), adenoviruses, adeno-associated viruses and lentivirus. Lentivirus-derived vectors are promising because they can infect both dividing and non-dividing cells.
    - Unlike wild type viruses, these vectors are engineered by deleting the essential genes that allow replication, assembling or infection.
    - In the next step, target cells such as the patient's liver or lung cells are infected with the viral vector. The vector then unloads its genetic material containing the therapeutic human gene into the target cell.
    - Generation of a functional protein product from the therapeutic gene restores the target cell to a normal state.
    - Besides virus-mediated gene delivery systems, the non-viral options for gene delivery include:
      - Direct inoculation of therapeutic gene into target cells—naked DNA (limited value).
      - Use of liposomes to carry the therapeutic gene to target cells.
      - Use of plasmids to carry the therapeutic gene to target cells.

Limitations of Vectors

- The main limitation of adenoviral vectors is the B-cell and T-cell-mediated inflammatory response resulting from an early activation of immune cells. Majority of the human population has been exposed to adenoviral infection and thus have antibodies against different serotypes.
- Other disadvantages of adenoviruses are their short-term expression and difficult or limited transduction of the cells.
- Important limitations of retroviral vectors include low vector titre, low transfection efficiency in *in vitro* experiments, particle instability and inability to transduce non-dividing post-mitotic cells. Therefore, the retroviral vectors are more suitable for *ex vivo* gene therapy.

Risks

- Potential for vectors producing disease by recombining with other viruses or getting activated by genes of host.
- May induce cancers when the vector and the genes to be transferred act together on a nearby proto-oncogene present in host.
- Genes that have been transferred (transgenes) can produce some risks after a long latency. Continuous, lifelong exposure to transgenes or vectors increases the probability of subtle toxic properties becoming manifest over the long term.
- Immune overreactions can occur, producing serious effects including autoimmunity and death.
- Leukaemia has been reported in treated patients.

Therapeutic Applications

- At present, gene therapy has not been approved for clinical use.
- Trials are going on for using gene therapy in the treatment of various genetic disorders, cancers, infectious diseases and other diseases like Alzheimer's disease and atherosclerosis.

Disturbances in Water, Electrolyte and Acid–Base Balance

Q. Give an account of the normal distribution of water in the body of an average adult male.

- Body water accounts for about 60% of the total body weight. Thus, a healthy 65-kg male has about 40 L of water.
- The body water can be divided into two main compartments:
  - Extracellular compartment that contains 25–40% of total water. This is called extracellular fluid (ECF).
  - Intracellular compartment that contains 60–75% of total water. This is called intracellular fluid (ICF).
- The extracellular compartment can be further divided into:
  - Vascular compartment.
  - Interstitial compartment in a ratio of 1:3.
- The distribution of body water in a 65-kg male can be represented as follows:
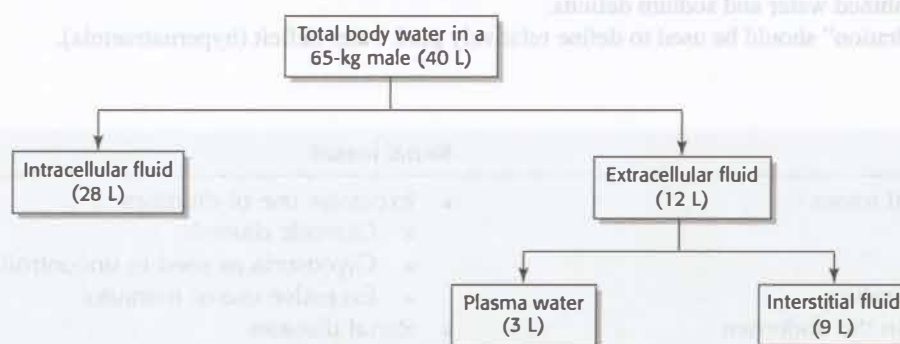
Q. Define ions, anions and cations. Name the important anions and cations in the human body.

- Ion is an atom or group of atoms with an electrical charge.
- Anion is a negatively charged ion. Examples of anions are: bicarbonate (HCO_3^-), chloride (Cl^-), phosphates, sulphates, organic acids and proteins.
- Cation is a positively charged ion. Examples of cations are: sodium (Na^+), potassium (K^+), calcium (Ca^{++}) and magnesium (Mg^{++}).

Q. What are the principal electrolytes in the fluid compartments?

Q. Specify the range of normal values of common electrolytes, pH and osmolality of blood.

- Sodium (Na^+) and chloride (Cl^-) are the principal electrolytes in the ECF compartment.
- Potassium (K^+) and phosphate are the principal electrolytes in the intracellular fluid (ICF) compartment.

Investigation	Normal range	Investigation	Normal range
Sodium (serum)	136–145 mmol/L	Magnesium (serum)	2–3 mg/dL
Potassium (serum)	3.5–5.0 mmol/L	pH of blood	7.38–7.44
Chloride (serum)	98–106 mmol/L	Bicarbonate (blood)	21–28 mmol/L
Calcium (plasma)	9–10.5 mg/dL	Osmolality (serum)	285–295 mOsm/kg water
Phosphorus (serum)	3–4.5 mg/dL		

Q. What do you understand by anion gap? Enumerate a few conditions associated with increased anion gap.

- Anion gap or delta (Δ) denotes the concentration of the unmeasured anions in the plasma—namely phosphates, sulphates, organic acids and protein anions.
- The following formula can be used to calculate the anion gap:

$$\text{Anion gap} = Na^+ - (Cl^- + HCO_3^-)$$

- The normal anion gap is 10–12 mmol/L.
- An increased anion gap is usually seen in some forms of metabolic acidosis. A few examples are given in the information box below:

• Diabetic ketoacidosis	• Salicylate poisoning
• Lactic acidosis	• Methanol poisoning
• Uraemic acidosis	• Ethylene glycol poisoning
• Isoniazid poisoning	• Iron poisoning

- Reduced anion gap is seen in lithium and bromide intoxications, and multiple myeloma.

Q. Describe the causes, clinical features, laboratory features and treatment of volume depletion.

- It represents combined water and sodium deficits.
- The term "dehydration" should be used to define relatively pure water deficit (hypernatraemia).

Causes

Extrarenal losses	Renal losses
• Gastrointestinal losses	• Excessive use of diuretics
• Vomiting	• Osmotic diuresis
• Diarrhoea	• Glycosuria as seen in uncontrolled diabetes
• Gastric aspiration	• Excessive use of mannitol
• Sequestration in the abdomen	• Renal diseases
• Peritonitis	• Salt-wasting tubular diseases
• Loss from skin	• Diuretic phase of acute renal failure
• Excessive sweating	• Chronic renal failure
• Burns	• Deficiency of mineralocorticoids
	• Addison's disease

Clinical Features

- The important clinical findings of volume depletion are dry skin and mucous membranes, reduced or absent tears, reduced skin turgor, tachycardia, shock, depressed fontanelles (in infants) and altered mental status.
- In patients with extrarenal losses, the urine output is reduced.

Laboratory Features

- Sodium concentration is normal, reduced or elevated depending upon the proportion of loss between water and sodium.
- Blood urea is often raised, particularly in severe volume depletion.
- Urinary sodium is important in differentiating renal from extrarenal losses. In renal and adrenal causes, urinary sodium is usually more than 20 mEq/L while it is less than 10 mEq/L in extrarenal losses.

Treatment

- Mild-to-moderate volume depletion is often due to gastroenteritis. This should be corrected by increasing oral intake of sodium and water, usually in the form of an oral rehydration solution.
- In severe cases, administer intravenous fluids, usually as normal saline or Ringer's lactate.

Q. What is hyponatraemia? Discuss its pathophysiology, causes, clinical features and treatment.

- Hyponatraemia indicates that the body fluids are diluted by excess of water relative to total solute and is defined as serum sodium <135 mEq/L.

Pathophysiology

- Most often, hyponatraemia is associated with a low serum osmolality (hypotonicity) caused by either retention of water or loss of sodium.
- In some cases, hyponatraemia occurs due to accumulation of solutes in the ECF (mannitol, glucose) where the osmolality is increased.
- Normally, a slight reduction in serum sodium results in suppression of ADH due to reduction in osmolality that causes excretion of dilute urine thereby normalising sodium. However, maintenance of hyponatraemia occurs because of following factors:
  - Excessive ingestion of water.
  - Reduced excretion of water by the kidneys due to renal failure.
  - Reduced excretion of water by kidneys due to inappropriate release of ADH [syndrome of inappropriate ADH secretion (SIADH)] or increased sensitivity to ADH.
  - Reduced renal excretion of water due to slow urine flow in the collecting tubules. This may occur if there is enhanced proximal tubular reabsorption of salt and water (as in congestive heart failure and cirrhosis of liver) that limits delivery of urine to the collecting tubules and because the volume is low, urine flows so slowly that it gets further concentrated without ADH requirement.

Effect of Hyponatraemia on Brain

- Within minutes after the development of hypotonicity water enters the brain causing its swelling and reduced osmolality.
- The brain volume is partially restored within a few hours due to loss of electrolytes from the brain cells. This is the rapid adaptation.
- Within next several days, the brain volume is normalized due to loss of organic compounds from the brain cells. This is the slow adaptation.
- Due to loss of solutes the brain, osmolality is low. Slow correction of hypotonicity produces gradual rise in brain osmolality without any risk. However, rapid correction of hyponatraemia produces loss of brain water resulting in brain damage.

Causes

Hyponatraemia with low osmolality	Hyponatraemia with raised osmolality

- Reduced effective blood volume
   - Increased ECF volume (oedema states)
     - Congestive heart failure
     - Nephrotic syndrome
     - Cirrhosis of liver
   - Reduced ECF volume (no oedema)
     - Renal loss of sodium (diuretics, ketonuria, Addison's disease)
     - Extrarenal sodium loss (sweating, vomiting, diarrhoea, peritonitis, pancreatitis)
 - Normal or increased effective blood volume
   - Syndrome of inappropriate secretion of ADH (SIADH)
   - Primary polydipsia
   - Chronic renal failure
	- Hyperglycaemia
	 - Mannitol administration

Clinical Features

- Hyponatraemia per se does not produce any significant clinical features. It causes decrease in cellular osmolality that is responsible for various features.
- These include muscle cramps, weakness and fatigue, mental confusion, disorientation, coma and convulsions.
- Speed of development and severity of hyponatraemia determine its clinical significance.

Treatment

- The most important dangers of rapid correction of hyponatraemia are vascular overload, shrinkage of brain (if the brain volume has already been normalised through loss of organic acids) and central pontine myelinolysis. The latter is characterized by quadriplegia with dysarthria and dysphagia with varying levels of consciousness.
- The rate of correction of hyponatraemia in a symptomatic patient should be around 0.6 mEq/L/hour. In severely symptomatic patients, it can be 4–6 mEq/L over 2–4 hour but total correction in a day should not exceed 8–10 mEq/L
- Correction of hyponatraemia requires either addition of sodium or removal of water or both. In most cases of acute hyponatraemia that require rapid correction, the cause of low sodium is excess water, and hence, removal of water is indicated.
- Removal of excessive water can be achieved by administration of a loop diuretic (which removes water and salt) and hypertonic saline (which adds salt). Under the action of loop diuretic, the urine is nearly isotonic. As the excretion of isotonic urine will not alter the serum sodium concentration significantly, the increase in sodium levels can be accurately estimated on the basis of the amount of sodium administered.
- When slow correction of hyponatraemia in a volume-expanded subject is desired, it is best to restrict the fluids. If this is not possible, use a loop diuretic and increase intake of salt and potassium.
- In patients with reduced ECF volume, priority is to restore intravascular volume by infusing normal saline.

Hypertonic Saline

- For symptomatic hyponatraemia in the form of seizures, altered mental status or coma, 3% hypertonic saline solution.
- For patients with chronic hyponatraemia, the rate of correction should not exceed 0.5 mEq/L/hour.
- For acute cases, the rate of correction may be 1–2 mEq/L/hour initially.
- Infusion rate of hypertonic saline should not exceed 1–1.5 mL/kg/hour and it should not be generally given for more than 3–4 hours. 1.2 mL/kg of hypertonic saline will raise sodium by about 1 mEq/L.
- Sodium levels rechecked at 2, 3 and 6 hours.

Vasopressin V2-Receptor Antagonists

- Tolvaptan, an orally active vasopressin V2-receptor antagonist promotes aquaresis––excretion of electrolyte-free water.
- Found to be useful in chronic hyponatraemia.
- Side effects include increased urine flow and thirst, and dry mouth.
- Intravenous agent is conivaptan that can be used in euvolaemic or hypervolaemic patients with hyponatraemia.

Q. Give a brief account of syndrome of inappropriate antidiuretic hormone secretion.

- Hypotonicity of the ECF normally shuts off the secretion of antidiuretic hormone (ADH). In syndrome of inappropriate antidiuretic hormone (SIADH) the secretion of ADH may continue "inappropriately" despite hypotonicity of the ECF.
- The cardinal features of SIADH are:
  - Hyponatraemia due to excessive water retention.
  - Urine osmolality inappropriately high (usually >100 mOsm/L).
  - Plasma osmolality <270 mOsm/L
  - Plasma urea and creatinine are normal or low.
  - Continued urinary sodium excretion (>40 mEq/L).
  - Clinically, normal intravascular volume (euvolaemia).
  - Both hypothyroidism and glucocorticoid deficiency excluded.

Causes

• Pulmonary causes	Small cell carcinoma, pneumonia, tuberculosis, COPD
• CNS causes	Meningitis, tumours, head injury, stroke
• Drugs	Chlorpropamide, tolbutamide, vincristine, cyclophosphamide, carbamazepine

Clinical Features

- Clinical features include nausea, irritability, confusion, seizures and coma. There is no oedema.

Treatment

- The underlying cause should be corrected.
- Fluid intake should be restricted to 500–1000 mL/day.

- Demeclocycline (ADH antagonist) may be given at a dose of 600–1200 mg/day.
- Slow infusion of hypertonic saline and frusemide may be rarely required in severe hyponatraemia.
- Rapid correction of slow-onset hyponatraemia may produce central pontine myelinolysis.

Q. Describe primary water depletion or hypernatraemia or dehydration.

- An elevation in the serum sodium concentration >145 mEq/L.

Pathophysiology

- Hypernatraemia is much less common than hyponatraemia because even a small increase in the serum sodium concentration is a potent stimulus to thirst.
- Elevated sodium concentration develops in those patients who are unable to experience thirst or are unable to gain access to water.

Effects of Hypernatraemia on Brain

- Within minutes after the development of hypertonicity, brain cells lose water causing shrinkage of the brain and an increase in osmolality.
- Rapid adaptation occurs within a few hours as electrolytes enter the brain cells causing partial increase in brain volume.
- Over several days, the brain volume becomes normal due to intracellular accumulation of organic compounds.
- Slow correction of the hypertonic state does not induce cerebral oedema as the accumulated solutes are gradually shifted out of the brain cells.
- In contrast, rapid correction may result in cerebral oedema as brain uptakes water from the relatively hypotonic ECF.

Causes

- Decreased intake	Coma, depression, inability to swallow
- Increased loss from skin	Fever, hyperthyroidism, hot environment
- Increased respiratory loss	Hyperventilation
- Increased loss in urine	Diabetes insipidus, medullary cystic disease

Clinical Features and Investigations

- Clinical features of hypernatraemia are due to increased osmolality and are same as that of diabetic hyperosmolar state.

Clinical features	Investigations
- Marked thirst	- Haematocrit usually >50%
- Muscle weakness, rigidity	- Raised blood urea levels
- Dry mouth	- Raised plasma sodium
- Mental confusion, coma	- Urine specific gravity >1.010
- Intracranial haemorrhage (in acute hypernatraemia)	- Polyuria and urine specific gravity <1.010 in diabetes insipidus
- Tachycardia and low systolic blood pressure	

Management

- In patients with gradual onset of water depletion over more than 2 days, correction should be done slowly as rapid lowering of sodium produces shift of water from ECF into brain cells. The rate of correction should not exceed 0.7 mEq/L/hour.
- When hypernatraemia is associated with hypotension due to volume depletion, the initial solution should be isotonic saline so as to increase the ECF volume. However, if neurological features are also present, therapy should be started with N/2 saline.
- Calculation of free water deficit:
  - Free water deficit is calculated as: Total body water x (plasma sodium/140 – 1)
  - In general, 50% of this calculated deficit is given over first 24 hours and the remaining over the next 24 hours

- As a rough guide, the following box shows the requirement of fluids in a 65-kg person:

Severity	Fluid and route of administration	Quantity and time for replacement
• Mild depletion (1–2 L deficit)	Water by mouth or 5% glucose IV	2 L, over 6–12 hours
• Moderate (2–4 L deficit)	5% Glucose IV	2–4 L, over 24 hours
• Severe (4–10 L deficit)	0.9% NaCl IV	1 L, over 1 hour
	5% Dextrose IV	3 L, over 2 hours
	5% Dextrose IV	4 L, over 24–48 hours

- Relief of thirst, urine output more than 1500 mL/24 hours and normal plasma sodium levels indicate adequate correction.

Q. What are the common causes of generalised oedema?

Q. Discuss the mechanism of oedema formation. How will you differentiate between cardiac, renal and hepatic oedema?

- Sodium and water excess results in a state of generalised oedema.

Causes

• Congestive heart failure	• Acute renal failure	• Severe malnutrition
• Nephrotic syndrome	• Chronic renal failure	• Drugs––Oestrogens, NSAIDs, corticosteroids, vasodilators, calcium channel blockers (e.g. amlodipine)
• Hepatic cirrhosis	• Pregnancy	
• Acute glomerulonephritis	• Protein-losing enteropathy	
• Hypothyroidism	• Chronic venous insufficiency	

Note: Amlodipine generally produces pedal oedema

Pathogenesis

- Oedema occurs when there is an imbalance between forces causing filtration of fluid and those causing absorption of fluid resulting in net filtration.
- It may be due to an elevation in capillary hydraulic pressure, an increase in capillary permeability or an increase in interstitial oncotic pressure, or due to a reduction in plasma oncotic pressure.
- Kidneys have a central role in maintaining body fluid homeostasis. They control ECF volume by adjusting sodium and water excretion.
- ADH which is secreted in response to stimuli such as changes in blood volume, tonicity and blood pressure is the primary regulator of body water.
- Effective arterial blood volume (EABV) correlates with ECF volume. It is sensed by volume homeostatic mechanisms that change renal sodium reabsorption.
- In healthy persons sodium loading increases ECF volume and EABV resulting in prompt natriuresis and restoration of normal volumes.
- In persons who are volume depleted, EABV and ECF volume are reduced which activate renin–angiotensin–aldosterone system resulting in renal sodium retention and restoration of normal blood volume.
- In oedematous states, there is reduction in EABV which activates sympathetic nervous system, renin–angiotensin–aldosterone axis and ADH secretion. Because of these compensatory mechanisms, oedema persists.
- Pathogenesis of oedema in the commonly encountered clinical conditions like congestive heart failure, nephrotic syndrome and hepatic cirrhosis are discussed.

Pathogenesis of Oedema in Heart Failure (Cardiac Oedema)

Reduced cardiac output

↓

Reduced arterial flow

↓

Reduced effective arterial blood volume (EBV)

↓

Stimulation of sympathetic nervous system   Stimulation of renin–angiotensin system

↓

Increased proximal tubular reabsorption of salt and water

↓

Reduced distal tubular sodium and water delivery

↓

Further water and sodium absorption (partly contributed by resistance to atrial natriuretic peptides)

↓

Increased salt and water in extracellular fluid

↓

Increased interstitial fluid ← Increased venous pressure (right-sided failure)

↓

Oedema

Pathogenesis of Oedema in Nephrotic Syndrome (Renal Oedema)

Proteinuria >3.5 g/day

↓

Low plasma albumin

↓

Reduced plasma colloid osmotic pressure

↓

Shift of water and electrolytes from intravascular to interstitial space

↓

Reduction in plasma volume

↓

Stimulation of sympathetic system   Stimulation of renin-angiotensin mechanism

↓

Increased aldosterone secretion

↓

Increased sodium and water retention

↓

Expansion of interstitial fluid volume → Oedema

Pathogenesis of Oedema in Hepatic Cirrhosis (Hepatic Oedema)

```
┌─────────────────┐                    ┌─────────────────┐
│ Decreased hepatic│                   │ Hepatic venous  │
│ albumin synthesis│                   │outflow obstruction│
└─────────────────┘                    └─────────────────┘
        │                                       │
        ▼                                       ▼
┌─────────────────┐                    ┌─────────────────┐
│ Hypoalbuminaemia│                    │Portal hypertension│
└─────────────────┘                    └─────────────────┘
        │                                       │
        ▼                                       ▼
┌─────────────────┐                    ┌─────────────────┐
│ Decreased plasma│                    │ Expansion of    │
│ oncotic pressure│                    │splanchnic circulation│
└─────────────────┘                    └─────────────────┘
        │                                       │
        └───────────────┬───────────────────────┘
                        ▼
        ┌──────────────────────────────────┐
        │ Decreased effective arterial blood volume │──────────┐
        └──────────────────────────────────┘                  │
                        │                                      │
                        ▼                                      │
        ┌──────────────────────────────────┐                  │
        │ Renal hypoperfusion              │                  ▼
        └──────────────────────────────────┘        ┌─────────────────┐
                        │                            │ Stimulation of  │
                        ▼                            │sympathetic system│
        ┌──────────────────────────────────┐        └─────────────────┘
        │ Activation of renin–angiotensin– │                  │
        │ aldosterone system               │                  │
        └──────────────────────────────────┘                  │
                        │                                      │
                        ▼                                      │
        ┌──────────────────────────────────┐                  │
        │ Renal retention of sodium and water │◄──────────────┘
        └──────────────────────────────────┘
                        │
                        ▼
        ┌──────────────────────────────────┐
        │ Increased plasma volume          │
        └──────────────────────────────────┘
                        │
                        ▼
        ┌──────────────────────────────────┐
        │ Transudation of fluid            │
        └──────────────────────────────────┘
                        │
                        ▼
        ┌──────────────────────────────────┐
        │ Oedema (including ascites)       │
        └──────────────────────────────────┘
```

Note: Ascites can also occur secondary to hepatic lymph weeping from the surface of the liver as a result of obstruction of the lymphatics by distorted hepatic architecture.

Clinical Features

- Cardiac oedema accumulates over dependent parts. In ambulant patients, it occurs symmetrically in the legs, particularly in the pretibial region and around the ankles. It is less in the morning and more towards the evening. Oedema is sacral in bedridden patients.
- Oedema of renal origin is classically identified by puffiness of the face, particularly around the periorbital region.
- In oedema of hepatic origin, the accumulation of fluid is predominantly manifested as ascites.

Management

- Treatment may be divided into primary and secondary.
- Primary treatment is directed at eliminating the cause of the problem—e.g. improvement of cardiac function, correction of hypoalbuminaemia.
- Secondary treatment is mainly concerned with correcting the salt and water overload. They include the following measures:
  - Restriction in sodium intake—dietary sodium should be restricted to about 50–100 mmol/day. A "no added salt diet", allowing salt only in cooking, with no addition of salt at table and avoidance of salty food is generally satisfactory.
  - Modest restriction of water intake to about 1000 mL/day should be advocated.
  - Diuretics should be given to increase rate of urinary excretion of sodium and water. Thiazide diuretics (e.g. hydrochlorothiazide 50–100 mg/day) may be used. More powerful loop diuretics (e.g. frusemide 40–120 mg/day) may be used in severe oedema. In severe renal failure or life-threatening pulmonary congestion, intravenous frusemide may be used.

Q. Discuss the normal physiology of potassium in the body.

- Potassium is the one of the major elements of ICF.
- Almost 98% of potassium present in ICF.
- Concentration in ECF varies between 3.5 and 5.0 mEq/L.
- Potassium is abundant in meat, oranges, lemon, grapes, bananas and dry fruit.

Physiology

- Potassium is the principle intracellular cation (ICF concentration is 150–160 mEq/L) and the concentration gradient between ECF and ICF is maintained by the Na^+ K^+-stimulated ATPase system.
- ECF potassium greatly influences the neuromuscular function as the latter is dependent upon the ratio of ICF to ECF potassium. As ECF potassium concentration is low, a small change in ECF potassium produces large change in this ratio, and hence, influences the excitability of the tissue. On the other hand, only a large change in ICF potassium is required to change the ratio significantly.
- For a loss or gain of 100–200 mEq, the plasma potassium reduces or increases by 1 mEq/L, respectively.
- An acute potassium load is actively taken by the tissue but within a few hours renal excretion of potassium increases. Because of this reason, sustained hyperkalaemia is rarely produced by increased ingestion of potassium.
- On the other hand, renal response of conserving potassium is sluggish when potassium intake is reduced. Excretion does not fall to minimal levels for 1–2 weeks and during this period of gradual renal adaptation around 200 mEq of potassium may be lost from the body.
- Renal excretion of potassium is mainly by secretion at the level of distal tubules and collecting ducts as filtered potassium is almost completely reabsorbed proximally. This secretion is influenced by aldosterone levels, distal tubular urine flow rate, acid–base status and potassium concentration of tubular cells.
  - In hyperkalaemia, potassium secretion is stimulated directly due to increased potassium concentration in the tubular cell and indirectly by increased aldosterone secretion.
  - Administration of loop diuretics enhances distal fluid flow that increases potassium secretion.
  - Acidosis reduces tubular secretion of potassium while alkalosis stimulates it.
- Metabolic changes influence the distribution of potassium in the body. Acidosis causes shift of potassium from ICF to ECF while alkalosis produces opposite effect.
- Insulin produces shift of potassium into ICF.

Q. What are the causes of hypokalaemia? Give a brief account of the clinical features, ECG manifestations and management of hypokalaemia.

Causes

• Loss from GI tract	Vomiting, diarrhoea, fistulae, villous adenoma, ureterosigmoidostomy, intestinal obstruction
• Loss in urine	Primary and secondary hyperaldosteronism, Cushing's syndrome, renal tubular acidosis, diuretics, hypomagnesaemia
• Intracellular shift of K^+	Alkalosis, high-dose insulin, periodic paralysis
• Reduced intake	Diet containing inadequate K^+, potassium-free IV fluids

Clinical Features

- Generalised muscle weakness and depression of tendon reflexes.
- Paralytic ileus.
- Rhabdomyolysis.
- ECG changes of hypokalaemia include flattening and inversion of T waves, sagging of the ST segment and appearance of U wave. T waves may disappear leading to apparent prolongation of QT interval (actually QU interval).
- Atrial and ventricular arrhythmias may occur, especially in patients receiving digitalis.
- Death may occur due to respiratory paralysis or cardiac arrest.

Treatment

- Treatment must be directed at correcting the hypokalaemia and eliminating the cause of potassium loss.
- Potassium supplementation can be given orally or intravenously in the form of potassium chloride (KCl).

- Patients with mild hypokalaemia with potassium between 3.0 and 3.5 mEq/L are usually asymptomatic and do not require urgent treatment. These patients should be advised to take a diet rich in potassium.
- Patients with moderate hypokalaemia with potassium between 2.5 and 3 mEq/L should receive oral potassium in a dose of 60–80 mEq/day in divided doses (20 mL of potassium chloride oral solution contains 15 mEq of potassium).
- If patient cannot tolerate oral potassium or GI losses are massive, intravenous potassium supplementation is required. Patients with symptomatic moderate or severe hypokalaemia with potassium <2.5 mEq/L also require intravenous potassium.
- Isotonic saline (500 mL) containing 20 mEq of potassium (as chloride) should be given over 2–3 hours. Repeated measurements of plasma potassium are necessary to determine whether further KCl is required. It is also preferable to monitor the patient using a cardiac monitor.
- Patients with hypomagnesaemia can be refractory to potassium replacement alone. These patients require both magnesium and potassium.

Q. What are the causes of hyperkalaemia? Discuss briefly the clinical features, ECG manifestations and management of hyperkalaemia.

Causes

Impaired excretion	Acute renal failure, severe CRF, Addison's disease, hypoaldosteronism, type 4 renal tubular acidosis, potassium sparing diuretics, angiotensin converting enzyme inhibitors, NSAIDs
Excessive intake	Intravenous fluids containing K^+, high K^+ foods
Tissue breakdown	Haemolysis, rhabdomyolysis, crush injury, burns, tumour lysis syndrome
Shift of K^+ out of cell	Acidosis, insulin deficiency, hyperkalaemic periodic paralysis, β-blockers, digitalis poisoning, succinylcholine
Pseudohyperkalaemia	Haemolysed blood sample, marked thrombocytosis

Clinical Features

- The common clinical features include cardiac arrhythmias, muscular weakness progressing to flaccid paralysis and respiratory embarrassment.
- Electrocardiographic manifestations of hyperkalaemia are:
  - Tall, peaked T waves.
  - Prolongation of PR interval.
  - Reduced height of P wave.
  - Prolongation of QRS complex.
  - "Sine wave" pattern.
- Terminally ventricular fibrillation and standstill may occur.

Management

- Identification and elimination of the underlying causes.
- When there are marked ECG changes, 10 mL of 10% calcium gluconate solution is given intravenously slowly over 2–5 minutes. It stabilises the myocardial cells.
- Intravenous administration of glucose along with insulin encourages shift of potassium from extracellular compartment to intracellular compartment.
  - 50 mL of 50% glucose plus 10 units of soluble (plain) insulin may be given intravenously as a bolus.
  - Alternatively, in moderate hyperkalaemia, 500 mL of 20% glucose plus 10 units of soluble insulin may be given as an infusion over 6–12 hours.
- Intravenous administration of 50–100 mL of 8.4% sodium bicarbonate is useful in renal failure patients with hyperkalaemia and acidosis.
- Nebulisation of β-agonists (salbutamol, terbutaline) also can reduce potassium levels by producing shift of potassium to intracellular compartment. Dose of salbutamol is 10–20 mg over 10 minutes and can be repeated every 2–6 hours.
- Cation exchange resins such as sodium polystyrene sulphonate are helpful in the removal of K^+. The resins can be given orally or as enema.
- If these measures fail, haemodialysis is indicated.

Q. Discuss briefly about physiology of acid–base balance.

Q. Describe various terms used in assessment of acid–base status of a patient.

Normal Physiology

- About 20,000 mmol of carbonic acid (from metabolism of carbohydrates and fats) and 80 mEq of non-volatile acids (from metabolism of dietary proteins) are produced daily. Despite this, the pH of ECF is maintained between 7.36 and 7.44. The defence against changes in pH is provided by three buffer systems: physiological buffers, pulmonary mechanisms and renal mechanisms.

Physiological Buffers

Bicarbonate–Carbonic Acid System

- Major physiological buffer.
- Bicarbonate is converted into water and carbon dioxide whenever H^+ ions are added. Carbon dioxide thus liberated is excreted by the lungs.
- Total buffering capacity of this system is about 15 mEq/L, which is sufficient for only 15–20 days. However, kidneys have the ability to regenerate bicarbonate and therefore help in maintaining the buffering capacity of the ECF.

Intracellular Proteins

- Haemoglobin is the most important of all intracellular proteins and can buffer large amounts of H^+ ions without disturbing the pH.
- In the red cells, carbon dioxide combines with water to form carbonic acid, which dissociates to produce H^+ ions that are buffered by haemoglobin.

Bone

- Contains large amount of bicarbonate and can buffer parts of acute acid load.

Pulmonary Mechanisms

- Carbon dioxide is the principal volatile acid of metabolism that is equivalent to potential carbonic acid.
- Normal concentration of carbon dioxide in the body is maintained around 1.2 mmol/L by the lungs. At this concentration, the pulmonary excretion equals the metabolic production of carbon dioxide.

Renal Mechanisms

- Kidneys reabsorb the filtered bicarbonate and also regenerate fresh bicarbonate.
- Bicarbonate is reabsorbed both in the proximal and distal segments by secretion of protons into the tubular fluid. For each molecule of bicarbonate filtered, one molecule is added to the blood by this mechanism.
- New bicarbonate is regenerated by secretion of protons onto urinary buffers. About one-third is titrated to phosphate while the remaining is secreted as ammonium.
- Rate of proton secretion by the kidneys is influenced by a number of factors:
  - Carbon dioxide tension.
    - Bicarbonate reabsorption is directly related to the ECF carbon dioxide tension. Hypercapnia stimulates and hypocapnia inhibits renal bicarbonate reabsorption.
  - Extracellular fluid volume.
    - Contraction of extracellular volume enhances renal bicarbonate reabsorption.
  - Aldosterone levels.
    - Hyperaldosteronism stimulates bicarbonate reabsorption by the kidneys and can lead to alkalosis.
  - Body potassium stores.
    - Severe hyperkalaemia produces increased H^+ secretion and therefore produces alkalosis due to increased bicarbonate reabsorption.

Evaluation of Acid–Base Status

- This is based on changes in the bicarbonate–carbonic acid system, and is described by the Handerson–Hasselbach equation:

$$pH = pK_a \times \log \frac{\text{Bicarbonate}}{\text{Carbonic acid}}$$

- pK_a is the dissociation constant and for carbonic acid–bicarbonate system and it is 6.1.
- Carbonic acid can be expressed as dissolved carbon dioxide and equals $\alpha \times pCO_2$, where α represents solubility coefficient and equals 0.031 mmol/L/mmHg of CO_2. At a pCO_2 of 40 mmHg, carbonic acid will be 1.2 mmol/L.
- The arterial blood gas analysers measure the pH and pCO_2 and bicarbonate concentration is calculated using the above-mentioned formula.
- By modifying the equation stated above, a more practical equation can be derived:
  - H^+ (nmol/L) = 24 × pCO_2/HCO_3 (at a pH of 7.4, H^+ concentration is 40 nmol/L).

Common Terms used in Evaluation of Acid–Base Status

- Acidosis means any disorder that adds acid or removes base from the body.
- Alkalosis means any disorder that adds alkali or removes acid from the body.
- Acidaemia indicates a disorder where pH is deceased.
- Alkalaemia means a disorder where pH is increased.
- Respiratory disorders are those where there is alteration in carbon dioxide concentration initially.
- Metabolic disorders are those that affect the bicarbonate concentration initially.
- Standard bicarbonate.
  - As plasma bicarbonate concentration is affected by changes in pCO_2, i.e. the respiratory disturbances, buffer base and standard bicarbonate have been used to indicate purely metabolic changes. Standard bicarbonate is the bicarbonate concentration in plasma in a completely oxygenated blood sample equilibrated with a pCO_2 of 40 mmHg at 37°C. A standard bicarbonate value below 24 mmol/L indicates metabolic acidosis and above 24 mmol/L metabolic alkalosis.
- Buffer base.
  - Represents the total equivalent concentration of all anionic (basic) buffer components of the blood, namely haemoglobin, bicarbonate, plasma proteins and phosphates. It is normally 48 mmol/L.
- Base excess or base deficit.
  - Base excess indicates the deviation of base buffer from its normal value. It can also be defined as the number of mmol of strong acid that is needed to adjust the pH to 7.4 when blood is equilibrated at a pCO_2 of 40 mmHg. It is calculated from pH, pCO_2 and haemoglobin. An increase in the amount of buffer base is termed as base excess while a decrease may be referred to as a base deficit or negative base excess.

Q. Discuss the causes, clinical features and management of metabolic acidosis.

- Metabolic acidosis is characterised by a reduction in plasma bicarbonate and a consequent rise in hydrogen ion concentration. The partial pressure of carbon dioxide is reduced secondarily by hyperventilation.
- Anion gap is due to the presence of unmeasured anions like albumin, sulphates, phosphates and organic acids. Increased accumulation of these unmeasured anions leads to acidosis with raised anion gap. In some patients of acidosis, there is an exchange of bicarbonate with chloride leading to loss of bicarbonate and hyperchloraemia. This leads to a normal anion gap with acidosis.

Causes

Increased anion gap
- Severe renal failure
- Increased production of organic acids
  - Diabetic ketoacidosis
  - Alcoholic ketosis
  - Starvation ketosis
  - Poisonings: methanol, salicylates, ethylene glycol, carbon monoxide, cyanide
  - Increased lactic acid production:
    - Cardiorespiratory arrest
    - Convulsions
    - Shock
    - Septicaemia
    - Liver failure

Normal anion gap (hyperchloraemia)
- Diarrhoea (loss of alkali)
- Potassium-sparing diuretics (renal tubular dysfunction)
- Renal tubular acidosis

Clinical Features

- In severe cases, there is deep sighing respiration (Kussmaul breathing or "air hunger").
- Peripheral vasodilatation and reduction in cardiac output may result in a fall in blood pressure.
- Severe acidosis may be associated with drowsiness, confusion and coma.
- Serum bicarbonate is low, blood pH is low and partial pressure of carbon dioxide is low.

Delta-Delta Gap

- Calculate delta-delta gap, if metabolic acidosis with an elevated anion gap is present.
- It distinguishes between a pure anion gap metabolic acidosis and a mixed acid-base disorder with both anion gap and non-anion gap acidosis.
- Delta-delta gap is calculated as follows:
  - Delta-delta gap = Delta anion gap – Delta bicarbonate
  (Delta anion gap is rise in anion gap from 12; delta bicarbonate is fall in bicarbonate from 24).
- In a pure anion gap metabolic acidosis, delta-delta gap should be approximate zero.
- If delta-delta gap is significantly positive, there is a metabolic alkalosis in addition to the anion gap metabolic acidosis.
- If delta-delta gap is significantly negative, there is a concomitant non-anion gap metabolic acidosis.

Treatment

- Main aim of treatment is to correct the underlying disorder.
- Sodium bicarbonate may be given in severe acidosis.
- In renal failure with metabolic acidosis, dialysis may be necessary.

Q. Give a brief account of metabolic alkalosis.

- Metabolic alkalosis is characterised by increased plasma bicarbonate, a fall in hydrogen ion concentration and a small compensatory rise in partial pressure of carbon dioxide.

Causes

Chloride-responsive (urine Cl⁻ <10 mEq/L)	Chloride-resistant (urine Cl⁻ >20 mEq/L)
• Vomiting • Gastric drainage • Diuretic use • Post-hypercapnia	• Mineralocorticoid excess—primary and secondary hyperaldosteronism, Cushing syndrome, use of glucocorticoids, liquorice ingestion
	Others • Excessive alkali ingestion

Clinical Features

- Specific clinical disturbances are rare. Acute alkalosis may induce tetany due to increased neuromuscular activity.

Treatment

- The underlying causes should be corrected.
- Normal saline administration is useful in chloride-responsive metabolic alkalosis.
- Potassium chloride supplementation is necessary in cases of alkalosis associated with hypokalaemia.

Q. Discuss respiratory acidosis.

- Respiratory acidosis occurs when the alveolar ventilation fails to keep pace with the rate of carbon dioxide production. As a result, the partial pressure of carbon dioxide rises, the hydrogen ion concentration increases and there is a compensatory rise in bicarbonate levels.
- Acute respiratory acidosis is found in acute type 2 respiratory failure. Here, the partial pressure of carbon dioxide is high and partial pressure of oxygen is low.

Causes

Disorders of gas exchange

Acute

- Severe asthma
- Acute exacerbation of obstructive lung disease
- Late stages of pulmonary oedema
- Foreign body inhalation
- Malfunctioning ventilators

Chronic

- Chronic obstructive lung disease

Disorders of musculoskeletal system

Acute

- Flail chest
- Tension pneumothorax or massive haemothorax
- Use of aminoglycosides

Chronic

- Myasthenia gravis
- Poliomyelitis

CNS and spinal cord abnormalities

Acute

- Overdose with opiates and sedatives
- Use of general anaesthetic agents
- Cardiac arrest
- Brain stem and cervical cord lesions

Chronic

- Central nervous system lesions

Clinical Features

- Severe respiratory acidosis is associated with confusion and obtundation. Papilloedema may occur due to raised intracranial pressure secondary to cerebral vasodilatation. Conjunctival suffusion may be present.

Treatment

- The underlying causes should be corrected. Rapid infusion of alkali is justified only in prolonged cardiopulmonary arrest.

Q. Discuss respiratory alkalosis and its causes.

- This occurs when there is excessive loss of carbon dioxide by hyperventilation of the lungs.
- Partial pressure of carbon dioxide and hydrogen ion concentration fall. Plasma bicarbonate is decreased.

Causes

Central mechanisms	Pulmonary mechanisms
- Anxiety	- Interstitial lung disease
- Fever	- Asthma
- CNS infections	- Pneumonia
- Cerebrovascular accident	- Congestive heart failure
- Metabolic encephalopathy	- Pulmonary embolism
- Septicaemia	
- Salicylate poisoning	
- Hepatic failure	

- In severe respiratory alkalosis, hyperventilation may be present. Sometimes, there may be manifestations of tetany.
- In acute respiratory alkalosis patients may complain of paraesthesiae, numbness, tingling and light-headedness.
- Treatment is elimination of the underlying disorder. In acute hyperventilation syndrome, sedation and rebreathing into a bag may terminate the attack.

Q. What are primary and compensatory responses to various acid–base disturbances?

Q. How will you evaluate acid-base disturbances?

Primary and Compensatory Responses in Various Acid–Base Disorders

Disorder	pH	Primary response	Compensatory response
• Metabolic acidosis	Decreased	Decreased HCO_3	Decreased pCO_2
• Metabolic alkalosis	Increased	Increased HCO_3	Increased pCO_2
• Respiratory acidosis	Decreased	Increased CO_2	Increased HCO_3
• Respiratory alkalosis	Increased	Decreased CO_2	Decreased HCO_3

Compensatory Responses in Acid–Base Disorders

Disorder	Compensation	Limit of compensation
• Metabolic acidosis	For every 1 mEq/L fall in HCO_3, pCO_2 falls by 1.2 mmHg	pCO_2 does not fall below 10 mmHg
• Metabolic alkalosis	For every 1 mEq/L rise in HCO_3, pCO_2 rises by 0.6 mmHg	pCO_2 does not rise above 55 mmHg
• Acute respiratory acidosis	For every 10 mmHg rise in pCO_2, HCO_3 rises by 1 mEq/L	HCO_3 does not rise above 30 mEq/L
• Chronic respiratory acidosis	For every 10 mmHg rise in pCO_2, HCO_3 rises by 3 mEq/L	HCO_3 does not rise above 45 mEq/L
• Acute respiratory alkalosis	For every 10 mmHg fall in pCO_2, HCO_3 falls by 2 mEq/L	HCO_3 does not fall below 18 mEq/L
• Chronic respiratory alkalosis	For every 10 mmHg fall in pCO_2, HCO_3 falls by 5 mEq/L	HCO_3 does not fall below 12 mEq/L

Evaluation of Acid–Base Disorders

- Step 1. Check the pH:
  - If pH < 7.36, acidosis is present.
  - If pH > 7.44, alkalosis is present.
- Step 2. Is primary process metabolic or respiratory? For this, check pCO_2 and HCO_3:
  - If pH < 7.36 and pCO_2 <40 metabolic acidosis.
  - If pH < 7.36 and pCO_2 >40 respiratory acidosis.
  - If pH > 7.44 and pCO_2 <40 respiratory alkalosis.
  - If pH > 7.44 and pCO_2 >40 metabolic acidosis.
- Step 3. Choose appropriate compensation for acid-base disorder as shown in the box above.
- Step 4. Determine if degree of compensation is appropriate or not:
  - If it is not, a second acid–base disorder is present which can be determined based on pCO_2 and HCO_3 levels.
- Step 5. If metabolic acidosis present, calculate the anion gap:
  - If the anion gap is elevated, an elevated gap metabolic acidosis is present.
- Step 6. If high anion gap acidosis, calculate delta-delta gap to determine if a second metabolic disorder present:
  - In a simple high anion gap metabolic acidosis, change in anion gap = decrease in bicarbonate, i.e. delta-delta gap is near zero.
  - If decrease in bicarbonate greater than rise in anion gap (i.e. delta-delta gap is significantly positive), concurrent non-anion gap metabolic acidosis is present.
  - If decrease in bicarbonate less than rise in anion gap (i.e. delta-delta gap is significantly negative), concurrent metabolic alkalosis is present.
- Step 7. Generate a differential diagnosis.

Chapter 16

Diseases of the Kidneys and Genitourinary System

Q. Describe a nephron with the help of a diagram. What are the functions of the kidney?
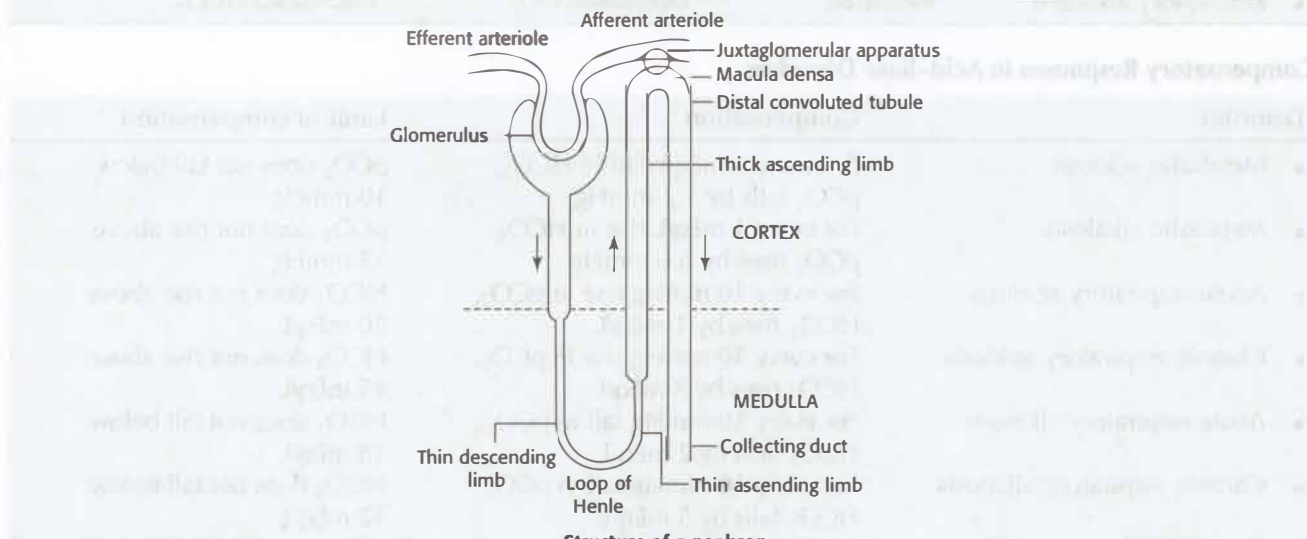
Structure of a nephron

- A nephron is the functional unit of the kidney. There are approximately 1 million nephrons in each kidney.
- The structure of a nephron is illustrated in the above diagram.

Functions of kidney	
• Excretory	Excretion of metabolic waste products, drugs
• Regulatory	Control of body fluid volume and composition, maintenance of acid–base balance
• Endocrine	Production of erythropoietin, renin, prostaglandins
• Metabolic	Metabolism of vitamin D

Q. Write a short note on the juxtaglomerular apparatus.

- The afferent arterioles and the distal convoluted tubules are in contact for a short distance. At this point the tubular cells become tall and columnar forming the macula densa.
- The wall of the afferent arteriole is thickened by specialised myoepitheloid cells (juxtaglomerular cells) that contain large secretory granules of renin.
- The macula densa, the juxtaglomerular cells and the lacis cells, which lie in between, constitute the juxtaglomerular apparatus. A diagrammatic representation of this is shown above.
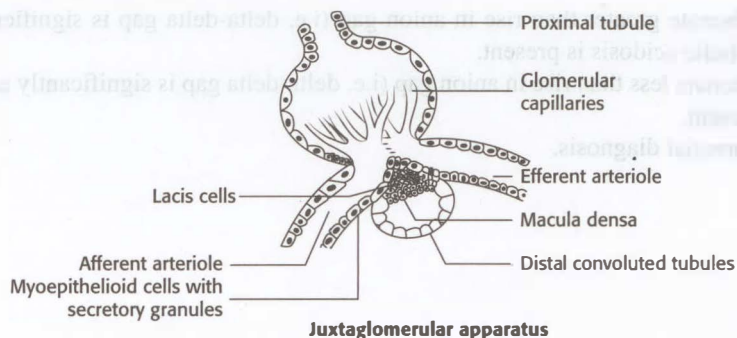
Juxtaglomerular apparatus

Renin

- Renin is produced and stored in the juxtaglomerular cells. Its release is controlled by the following factors:
  - Pressure changes in the afferent arteriole
  - Sympathetic tone
  - Chloride concentration in the distal convoluted tubule
  - Local prostaglandin release.
- Renin acts on angiotensinogen in the blood to form angiotensin I.
- Angiotensin I is converted to angiotensin II by angiotensin-converting enzyme (ACE).
- Angiotensin II is both a vasoconstrictor and an important stimulus for the release of aldosterone by the adrenal cortex.

Q. What is meant by azotaemia, oliguria and anuria? Enumerate the causes of oliguria and anuria.

- Azotaemia is a term used to denote an increase in the concentration of urea and creatinine in the blood, which occurs as a result of a fall in the glomerular filtration rate (GFR).
- Oliguria refers to the production of insufficient urine to enable solute to be excreted in adequate amount, and is usually less than 400 mL of urine/day (in an adult of average size). Causes of oliguria are given in the information box.

Pre-renal factors	Renal parenchymal diseases
- Hypovolaemia	- Acute glomerulonephritis
- Shock	- Acute tubular necrosis (ATN)
- Congestive heart failure	- Acute interstitial nephritis
- Cirrhosis	
- Peritonitis	
- Pancreatitis	

- Anuria refers to complete cessation of urine flow. Some authorities define anuria as a daily urinary output less than 100 mL. Anuria more commonly indicates obstruction of the outflow from both kidneys. Causes of anuria are given in the information box. Occasionally, diseases producing oliguria can produce anuria.

Causes of anuria
- Bilateral ureteric obstruction
- Prostatic or urethral obstruction
- Bilateral renal arterial or venous occlusion

Q. What is meant by polyuria? Enumerate the common causes of polyuria.

- The term polyuria denotes persistent increase in urine volume of more than 3 L/day, but this should be qualified to exclude normal individuals who desire a large fluid intake, and therefore, form large volumes of urine.

Causes of polyuria	
- Osmotic diuresis	Hyperglycaemia, administration of mannitol
- Concentration disorders	Diabetes insipidus, papillary necrosis, diuretic phase of ATN
- Drugs	Diuretics, lithium, alcohol
- Excessive water intake	Psychogenic polydipsia

Q. What is meant by proteinuria? What is microalbuminuria?

Q. Discuss Tamm–Horsfall mucoprotein.

- Pathological proteinuria is the urinary excretion of more than 150 mg of protein/day. Normal adults may excrete up to 150 mg of proteins daily. Pathological proteinuria may be "mild" (<1.0 g/day), "moderate" (1.0–3.5 g/day) or "massive" (>3.5 g/day).
  - Tubular proteinuria
    - Occurs in diseases affecting tubulointerstitial component of kidneys.
    - Usually has low molecular weight proteins (e.g. beta-2 microglobulin).
    - Amount of proteinuria is <2 g/day.

- Overflow proteinuria
  - Most commonly associated with increased production of abnormal low molecular weight proteins (e.g, light chains in multiple myeloma, myoglobin in rhabdomyolysis).
- Glomerular proteinuria
  - Physiological—associated with fever or heavy exercise.
  - Pathological—associated with glomerular pathologies.
- Microalbuminuria (also known as moderately increased albuminuria). Normal urine contains albumin in a concentration of less than 30 mg/L. Elevation of albumin in the urine from >30 to <300 mg/day (>20 to <200 µg/minute)—microalbuminuria—is so named because conventional dipstick tests cannot detect albumin levels of 30–300 mg/day.
  - Since it is often difficult to obtain 24-hour urine, measurement of urinary albumin concentration to urinary creatinine concentration ratio in an untimed spot urine sample is used in clinical settings (cutoff value >30 mg/g).
  - It is known to be an early indicator of diabetic glomerular disease (elevated fractional excretion of magnesium is a more sensitive marker than microalbuminuria in detecting early diabetic nephropathy).
  - It is an established risk marker for the presence of cardiovascular disease (coronary artery disease, peripheral artery disease and stroke) even in normotensive persons, and predicts progression of nephropathy when it increases to frank albuminuria (>300 mg/day).
  - Microalbuminuria can be reduced, and progression to overt proteinuria is prevented or retarded by aggressive blood pressure reduction, especially with ACE inhibitors or angiotensin receptor blockers, and control of diabetes.
  - Blood pressure levels should be maintained at or below 140/90 mmHg in anyone with diabetes or kidney disease.
- Tamm–Horsfall mucoprotein (also known as uromodulin) is a urine protein that is a normal constituent of urine. It does not arise from the plasma, but is produced in the thick ascending limb of the loop of Henle, and is excreted at a rate of 25 mg/day.
  - Its function is unclear. It may have some immunomodulatory activity and may protect against urinary tract infection (UTI).
  - It is a constituent of all types of urinary casts. Implicated in the pathogenesis of cast nephropathy, a form of renal failure associated with multiple myeloma in which intratubular casts occlude the flow of urine.

Q. Enumerate the common causes of haematuria. How will you clinically localize the site of bleeding?

- Haematuria may be macroscopic (visible on gross examination) or microscopic (three or more red blood cells per high-power field).
- The common causes of haematuria are illustrated in the diagram.

Causes of haematuria
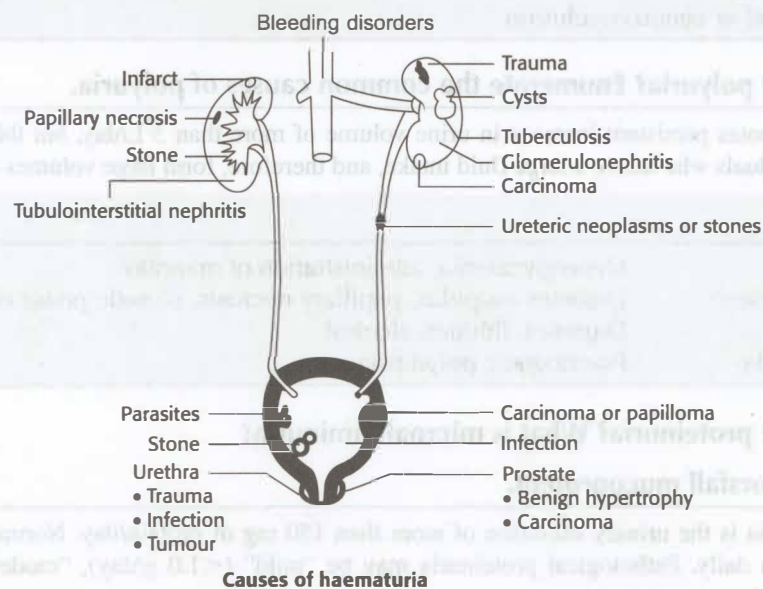
- The following features may help to localize the site of bleeding from the urinary tract:
  - When blood is seen at the start of voiding and then the urine becomes clear, bleeding from the urethra is suggested.
  - When blood is diffusely present throughout the urine, it may suggest bleeding from the bladder or above.

- Blood only at the end of micturition suggests bleeding from the prostate or bladder base.
- Haematuria of glomerular origin is described as cola coloured, while haematuria from renal pelvises and lower urinary tract is usually pink or red.
- Associated pain may indicate UTI, pyelonephritis (costovertebral tenderness) or renal calculus.
- Family history of haematuria may indicate Alport's syndrome, polycystic kidney disease or sickle cell disease.
- The presence of red-cell casts in the urine is diagnostic of bleeding from the kidney, most often due to glomerulonephritis.
- Dysmorphic erythrocytes upon urine examination are characterised by an irregular outer cell membrane, and suggest haematuria of glomerular origin.
- Acanthocytes (ring-formed erythrocytes with one or more membrane protrusions of variable size and shape) represent an early form of dysmorphic erythrocytes and are a marker for haematuria of glomerular origin.
- Erythrocytes of uniform character are classified as isomorphic and suggest haematuria of lower urinary tract origin. Microscopic clots of clumped erythrocytes in urine are also suggestive of lower urinary tract bleeding.

Q. What are the causes of painless haematuria? How will you evaluate such a patient?

Causes of painless haematuria	
• Kidney	Glomerulonephritis, infective endocarditis, renal tuberculosis, benign familial haematuria, IgA nephropathy, severe acute pyelonephritis, papillary necrosis (more common in diabetes mellitus and sickle cell trait or disease), renal cell carcinoma, microscopic polyangiitis, Wegener's granulomatosis, polycystic kidney disease
• Ureter	Neoplasms
• Bladder	Neoplasms, trauma, schistosomiasis
• Prostate	Prostatitis, neoplasms
• Urethra	Trauma

Patient's Evaluation

History

- History of recurrent visible haematuria.
- Age over 40 years.
- Current smoker or recent history of smoking.
- History of recurrent urinary tract infection (UTI) or other urological disorders.
- Occupational exposure to chemicals or dyes.
- Previous pelvic irradiation.
- History of excessive analgesic use.
- Treatment with cyclophosphamide.
- Use of anticoagulant and antiplatelet medicines more likely to exacerbate rather than cause, haematuria.
- History to suggest site of bleeding (refer above).

Examination and Investigations

- Blood pressure
- Cardiovascular examination
- Abdominal examination and prostatic evaluation
- RBC morphology (assessed by phase contrast microscopy of fresh urine)
- Proteinuria
- Renal function tests
- Platelet count and coagulation studies
- Ultrasound for kidneys, ureters, bladder and prostate
- Urine for acid-fast bacilli
- Urine cytology if risk factors for renal tract cancer present (smoking, analgesic abuse, industrial toxin exposure like aniline, benzidine, aromatic amines, age >40 years, pelvic irradiation, urinary schistosomiasis)
- Autoantibodies (ANA, ANCA)
- Intravenous pyelography
- Cystourethroscopy
- Computed tomography intravenous pyelogram

Q. Describe creatinine clearance or renal clearance.

- Renal clearance gives an estimate of the glomerular function of the kidney.
- Renal clearance is measured by using the following formula:

$$C = UV/P$$

C is the renal clearance;
U is the urinary concentration of any substance;
P is the plasma concentration of the same substance; and
V is the minute volume of urine.

- The polysaccharide, inulin, has been found to pass freely through the glomerular capillary wall. Inulin is neither absorbed nor excreted by the tubules, and hence, the quantity of inulin excreted in urine (UV) is identical with the amount filtered by the glomeruli. Therefore, the renal clearance of inulin can be used to estimate the GFR.
- The GFR for an average adult is about 125 mL/minute.
- In clinical practice, the measurement of creatinine clearance, which approximates to that of inulin, indicates the GFR.
- An estimate of GFR utilizing creatinine clearance is obtained by measuring the creatinine in a 24-hour urine sample, the plasma concentration of creatinine and substituting the measured values in the above formula. However, due to creatinine excretion via renal tubular secretion, the measurement of creatinine clearance using above formula tends to overestimate the true level of GFR.
- Creatinine clearance (and hence GFR) can also be calculated by using the Cockcroft–Gault formula if serum creatinine is stable:
  - Cl_{Cr} (mL/minute) = (140 – age) × Ideal body weight/72 × Serum creatinine (mg/dL) (for females, the value is multiplied by 0.85).
- Another method to calculate GFR is measurement of serum cystatin C, a low-molecular-weight protein that is a member of the cystatin superfamily of cysteine protease inhibitors.

Q. Discuss the role of ultrasonography in the diagnosis and management of renal diseases.

- This is the method of choice for assessing overall renal size and distinguishing solid tumours from cysts.
- Renal ultrasound can demonstrate dilatation of the pelvicalyceal system, which may be due to obstruction.
- Perinephric abscess, haematomas or calculi may be demonstrated.
- Renal biopsy and cyst puncture can be done under ultrasound screening.
- It is an excellent screening test for polycystic kidney disease.
- In malignant renal tumours, renal ultrasound can give additional information regarding extension of the tumour to renal veins, vena cava, lymph nodes or liver.
- The prostate size and bladder capacity can also be assessed.

Q. Give a brief account on acute glomerulonephritis or acute nephritic syndrome.

Q. Discuss the aetiology, pathogenesis, clinical features, diagnosis, complications and management of acute post-streptococcal glomerulonephritis.

- The term glomerulonephritis signifies glomerular inflammation in which there is an immunologically-mediated injury to the glomeruli.

Aetiology

Causes of glomerulonephritis	
- Infectious diseases (post-infectious glomerulonephritis)	Post-streptococcal glomerulonephritis (PSGN), infective endocarditis, syphilis, mumps, measles, hepatitis B, infectious mononucleosis, Epstein–Barr virus infection, malaria, HIV-associated nephropathy
- Multisystem diseases	Systemic lupus erythematosus, Goodpasture's syndrome, Henoch–Schonlein purpura, microscopic polyangiitis, Wegener's granulomatosis, sickle cell nephropathy
- Primary glomerular diseases	Diffuse proliferative glomerulonephritis, IgA nephropathy, mesangiocapillary glomerulonephritis, crescentic glomerulonephritis, membranous glomerulonephritis, focal segmental glomerulosclerosis
- Miscellaneous	Malignancy, eclampsia, D-penicillamine

Pathogenesis

- Two chief pathogenetic mechanisms are recognized:
  - Deposition of antigen–antibody complexes (immune complexes) in the glomeruli can result in glomerular disease.
  - Deposition of an antibody in the glomerular basement membrane, which then reacts with an antigen in the basement membrane causing glomerulonephritis.
- Normally, the immune complexes formed in the body are removed by the host's reticuloendothelial system. Impaired ability on the part of the host to clear the immune complexes may result in their deposition in the glomerular capillary walls.
- The antigen involved in the immune complex formation may be exogenous [e.g. bacteria such as streptococci as in post-streptococcal glomerulonephritis (PSGN)] or endogenous (e.g. antibodies to host DNA in patients with SLE)].
- The immune complexes and antibodies against a glomerular antigen may trigger injury by following mechanisms:
  - Complement activation
  - Fibrin deposition
  - Platelet aggregation
  - Release of cytokines and free oxygen radicals.

Clinical Features

- Acute nephritic syndrome is characterised by the acute onset of the following features:

Acute nephritic syndrome	
• Haematuria	• Hypertension
• Red blood cell casts	• Proteinuria
• Oliguria	• Uraemia
• Oedema	

- Asymptomatic patients are primarily characterised by microscopic haematuria

Post-Streptococcal Glomerulonephritis

- One of the common causes of acute nephritic syndrome is acute post-streptococcal glomerulonephritis (PSGN).
- PSGN occurs after a pharyngeal or cutaneous infection with nephritogenic strains of group A β-haemolytic streptococcus.
- Can occur following epidemics of infection or sporadic infections.
- There is a latent period between the streptococcal infection and the onset of nephritis. Following pharyngeal infection the latent period is about 6–21 days. Cutaneous infections are associated with longer latent period of about 3-6 weeks.
- Children are commonly affected.
- PSGN is commonly associated with poor personal hygiene, overcrowding and skin diseases like scabies.
- Onset is often abrupt with puffiness of face, oliguria, smoky urine or reddish urine, hypertension and oedema.
- The oedema of acute glomerulonephritis tends to appear initially in areas of low tissue pressure (periorbital areas), but subsequently progresses to involve dependent portions of the body, and may lead to ascites and/or pleural effusion.

Investigations

- Investigations in acute PSGN are given in the following box:

Investigations	Positive findings
• Urine microscopy	Red cells (particularly dysmorphic—i.e. distorted and fragmented red cells), red cell casts
• Cultures	Throat swab and swab from inflamed skin may grow group A β-haemolytic streptococci
• Antistreptolysin-O (ASO) titre	Elevated
• C3 level (complement)	May be reduced
• Urinary protein	Increased
• Urea and creatinine	May be elevated
• Renal biopsy	Features of glomerulonephritis

Treatment

- Treatment of acute PSGN is supportive.
- The measures include rest, salt restriction, diuretics and antihypertensives.
- Antibiotics are given for presumed throat infection as this may result in milder form of nephritis. Further, treatment of a carrier state may prevent spread to other household members.
- Dialysis is required in severe oliguria, fluid overload and hyperkalaemia.
- Steroids and cytotoxic drugs are of no value.
- Complications include pulmonary oedema, hypertensive encephalopathy and renal failure.

Prognosis

- Majority of children and adults with the epidemic form of PSGN have an excellent prognosis. However, some patients develop persistent urine abnormalities or hypertension.
- Conversely, up to 60% of adults with sporadic infections experience progressive irreversible renal damage.

Prevention

- Early eradication of pharyngitis-associated group A streptococci by use of antibiotics protects against glomerulonephritis.

Q. What is IgA nephropathy? Explain in brief.

- Also known as Berger's disease.
- Characterised by predominant IgA deposition in the glomerular mesangium.
- Presents with painless haematuria, generally within 1–2 days of upper respiratory infection.
- More common in children and young adults with peak incidence between 15 and 30 years.
- May be detected on routine urine examination (microscopic haematuria).
- Occasionally presents as acute renal failure (ARF) or nephritic syndrome.
- Diagnosis by renal biopsy.
- Up to 20% of patients have progressive disease, leading eventually to end-stage renal disease. In most such cases, rate of progression of disease is usually very slow. Clinical features that mark a poor prognosis include moderate to severe degrees of proteinuria, renal insufficiency at the time of renal biopsy, hypertension and certain features on kidney biopsy.
- Complete remission uncommon.
- Henoch–Schonlein purpura is a systemic disease which may have mesangial IgA deposition. It is more common during childhood as compared to IgA nephropathy
- No specific therapy is available. Aggressive therapy is not warranted in patients who are not likely to have progressive disease, or who have diffuse glomerulosclerosis on biopsy, or those who have stage 4 or 5 chronic kidney disease (CKD).
  - Therapeutic options include ACE inhibitors if significant proteinuria is present; also for control of hypertension.
  - Use of immunosuppressives is controversial. A 6-month course of corticosteroids may be tried in patients with persistent proteinuria >1 g/day despite 3–6 months of supportive care and blood pressure control.

Q. Briefly outline the causes, clinical features, investigations and treatment of rapidly progressive glomerulonephritis.

Q. Describe crescentic glomerulonephritis.

- Rapidly progressive glomerulonephritis (RPGN) is defined as any glomerular disease characterised by extensive crescents (usually >50%) as the principal histologic finding and by a rapid loss of renal function (usually a 50% decline in the GFR within 3 months).
- A crescent is the accumulation of cells and extracellular material in the urinary space of a glomerulus. The cells are parietal and visceral epithelium as well as monocytes and other blood cells.
- RPGN is classified pathologically into three categories:
  - Antiglomerular basement membrane (GBM) antibody disease—linear deposits of antibodies on immunofluorescence.
  - Immune-complex disease—granular deposits of immune complexes on immunofluorescence.
  - Pauci-immune disease (generally antineutrophil cytoplasmic antibody positive—ANCA positive)—little or no deposits on immunofluorescence.

Causes of Rapidly Progressive Glomerulonephritis

Anti-GBM antibody
- Goodpasture syndrome
- Anti-GBM disease (only kidney involvement)

Pauci-immune
- Wegener granulomatosis
- Microscopic polyangiitis
- Renal-limited necrotizing crescentic glomerulonephritis
- Churg–Strauss syndrome

Immune complex
- Post-infectious
- Post-streptococcal
- Visceral abscess
- Collagen vascular disease
- Lupus nephritis
- Henoch–Schönlein purpura
- Mixed cryoglobulinaemia
- Primary renal disease
- IgA nephropathy
- Membranoproliferative glomerulonephritis
- Idiopathic

Clinical Features

- Presents with moderate proteinuria, haematuria, oliguria, oedema and uraemia.

Investigations

- Leucocytosis and anaemia.
- Blood urea and serum creatinine levels usually elevated.
- Urinalysis shows modest proteinuria (1–4 g/day), microscopic haematuria, and RBC and WBC casts.
- Complement levels (C3 and C4) may be decreased in patients with immune-complex mediated RPGN.
- Circulating anti-GBM antibodies in Goodpasture syndrome.
- ANCA in patients with pauci-immune RPGN.
- Serum cryoglobulin levels may be elevated in cryoglobulinaemias.
- Abdominal ultrasound shows normal-sized kidneys.
- Chest X-ray in patients with Goodpasture syndrome and vasculitides may show diffuse opacities if pulmonary haemorrhage occur.
- Kidney biopsy.

Treatment

- Supportive therapy.
  - Control of infection
  - Control of volume status (dialysis if required).
- Specific therapy.
  - Immunosuppressive therapy (e.g. glucocorticoids, cyclophosphamide, azathioprine, mycophenolate), plasma exchange (in patients presenting with life-threatening pulmonary haemorrhage). Treatment of choice in anti-GBM antibody disease is plasmapheresis combined with prednisolone and cyclophosphamide.
  - Infliximab and rituximab.

Q. Discuss the aetiology, pathogenesis, clinical features, diagnosis and management of nephrotic syndrome.

- The nephrotic syndrome is characterised by the following abnormalities:

• Proteinuria (>3.5 g in 24 hours)	• Generalised oedema
• Hypoalbuminaemia	• Hyperlipidaemia

Pathogenesis

- In nephrotic syndrome, the permeability of the glomerular capillary wall is increased by glomerular inflammation, change in the surface electrical charge, and an alteration in the pore size. These result in excessive leakage of plasma proteins across the glomerular capillary wall into the urine, leading to hypoalbuminaemia.
- The decreased concentration of albumin in the blood leads to a decrease in plasma colloid oncotic pressure resulting in a disturbance in the Starling forces acting across peripheral capillaries. Intravascular fluid migrates into the interstitial tissue and causes oedema.

- The hypovolaemia also triggers the renin–angiotensin–aldosterone system. This causes increased reabsorption of sodium and water by the kidney, resulting in oedema.
- The low plasma colloid oncotic pressure also appears to stimulate hepatic lipoprotein synthesis. Hence, hyperlipidaemia (elevations of total plasma cholesterol, triglyceride, very-low-density lipoprotein and low-density lipoprotein) is also associated with nephrotic syndrome. It increases the risk of atherosclerosis and cardiovascular disease.

Consequences of Protein Loss

- Hypoalbuminaemia can lead to oedema and increased susceptibility to infections. May also produce pleural effusion and ascites. Subungual oedema may manifest as parallel white lines in the fingernail beds.
- Urinary losses of plasma proteins like thyroxine binding globulin can cause abnormalities in thyroid function tests.
- Deficiency of antithrombin III (due to urine loss) may produce a hypercoagulable state and renal vein thrombosis. Other reasons for hypercoagulable state include altered activity and levels of proteins C and S, increased hepatic synthesis of fibrinogen, and increased platelet aggregation.
  - In adults, most thromboses are venous, while in children arterial thromboses are more common.
  - Patient with acute renal vein thrombosis can present with sudden onset of flank or abdominal pain, gross haematuria and an acute decline in renal function, but most patients are asymptomatic.
  - Other consequences of hypercoagulable state include pulmonary embolism, myocardial infarction and stroke.
- Loss of globulins in urine may result in severe IgG deficiency leading to spontaneous bacterial peritonitis.
- Loss of cholecalciferol-binding protein may lead to vitamin D deficiency state.
- Loss of transferrin may result in microcytic hypochromic anaemia.
- Loss of metal binding proteins may result in trace metal deficiency—e.g. zinc, copper.
- Loss of drug binding proteins results in altered drug pharmacokinetics.

Causes of Nephrotic Syndrome

Primary (idiopathic)
- Idiopathic glomerular diseases like minimal change disease, membranous glomerulonephritis, mesangial proliferative glomerulonephritis, focal and segmental glomerulosclerosis (FSGS), and mesangiocapillary glomerulonephritis

Secondary

• Infections	Bacterial endocarditis, malaria, syphilis, hepatitis B, leprosy, HIV infection
• Connective tissue diseases	SLE, rheumatoid arthritis
• Neoplasms	Hodgkin's lymphoma, carcinomas, leukaemias
• Drugs and toxins	Penicillamine, captopril, gold, mercury, contaminated heroin
• Metabolic	Diabetes mellitus, amyloidosis

- Minimal change disease:
  - Most common cause of nephrotic syndrome in children (80%); responsible for 20% of all cases in adults.
  - Normal-appearing glomeruli on light microscopy of a renal biopsy specimen.
  - Effacement of foot processes of epithelial cells on electron microscopy.
- Focal and segmental glomerulosclerosis (FSGS):
  - Accounts for one-third of cases of nephrotic syndrome in adults.
  - May be idiopathic or develop secondary to HIV infection, heroin use, sickle cell disease, obesity and reflux nephropathy.
  - Patients usually present with nephrotic-range proteinuria, hypertension, renal insufficiency and occasionally haematuria.
- Membranous glomerulonephritis:
  - One of the most common primary renal causes of nephrotic syndrome in adults.
  - Male predominance.
  - Incidence usually peaks between ages 30 and 50 years.
  - Secondary causes in about 20–30% cases that include systemic lupus erythematosus, hepatitis B, malignancy or drug-induced (e.g. chronic gold or penicillamine drug therapy).
  - Approximately 75% of patients present with nephrotic-range proteinuria and 50% present with microscopic haematuria.

Investigations

- Investigations in nephrotic syndrome include a 24-hour urinary protein estimation, and estimation of serum albumin and serum cholesterol concentrations. Red cells and red cell casts may be present in the urine. However, in

minimal change disease RBCs and red cell casts are not present. Renal biopsy may be required to make a histological diagnosis.

- For suspected secondary causes appropriate investigations are required.

Management

- Treatment of nephrotic syndrome involves three steps:
  - Measures to reduce proteinuria
  - Measures to control complications of nephrotic syndrome
  - Treatment of underlying cause

Measures to Reduce Proteinuria

- These are required if immunosuppressive drugs and other specific measures against the underlying cause do not benefit the patient.
- ACE inhibitors reduce proteinuria and also slow the rate of progression of renal failure by lowering the intraglomerular pressure. This also prevents development of haemodynamically mediated focal segmental glomerulosclerosis.
- NSAIDs also reduce proteinuria in some patients but their use must be weighed against the risk of producing ARF, hyperkalaemia, and salt and water retention.

Measures to Control Complications of Nephrotic Syndrome

- Oedema should be controlled by salt restriction, rest and judicious use of diuretics. The weight loss should not exceed 1 kg/day. Aggressive diuresis may precipitate ARF due to reduction in intravascular volume.
- In severe cases, intravenous salt-poor albumin may be used as a temporary measure to reduce oedema. However, most of infused albumin will be excreted by the kidneys in 24–48 hours.
- Dietary proteins should be about 0.8–1.0 g/kg as excessive proteins in the diet may hasten the progression of renal disease. However, malnutrition should be prevented.
- Vitamin D supplementation in patients with biochemical evidence of vitamin D deficiency.
- Hyperlipidaemia should be controlled with dietary restrictions and lipid-lowering drugs.
- Anticoagulants are indicated in patients with deep venous thrombosis or arterial thrombosis.

Measures to Treat the Underlying Disease

Minimal Change Disease

- Children with nephrotic syndrome due to minimal change disease require initial treatment with corticosteroids in the form of daily prednisolone at a dose of 60 mg/m^2 (1 mg/kg body weight in adults) for 4 weeks. This is followed by alternate day prednisolone at a dose of 35 mg/m^2 (1 mg/kg in adults) for four additional weeks. Children who respond within the first 4 weeks of steroid treatment are termed "steroid responsive". Those who relapse on withdrawal of steroid are termed "steroid-dependent". Such relapses are retreated with the same initial regimen, but with more gradual withdrawal of prednisolone. Some patients may require low maintenance doses (5–10 mg/day) for 3–6 months.
- Patients who have frequent relapses or develop unacceptable corticosteroid side effects may be benefited by a brief course of cyclophosphamide (2 mg/kg/day) for 6 weeks. Other options include mycophenolate mofetil, calcineurin inhibitors such as cyclosporin and tacrolimus, and rituximab.
- Prognosis of patients with minimal change disease is excellent, though it has a characteristic remitting and relapsing course.

Focal and Segmental Glomerulosclerosis

- Steroids may be beneficial in only 20–30% cases.
- Cyclophosphamide, tacrolimus and cyclosporin may be of some benefit in steroid-resistant cases.

Membranous Glomerulonephritis

- Spontaneous remission may occur in 40% cases.
- Another 30–40% cases remit and relapse repeatedly.
- Rest 10–20% patients develop progressive renal failure. Steroids alone are not useful. Cyclophosphamide, cyclosporin and chlorambucil in combination with steroids may retard the progression in this subset of patients.

Q. Discuss the aetiopathogenesis, clinical features, investigations and management of urinary tract infection.

Q. Give a brief account of vesicoureteric reflux.

- UTI may be anatomically subdivided into lower tract infections (urethritis, prostatitis and cystitis) and upper tract infections (pyelonephritis and perinephric abscess).
- UTI is associated with multiplication of organisms in the urinary tract and is defined by the presence of more than 10^5 organisms/mL in the midstream sample of urine (MSU). This is denoted as "significant bacteriuria". The clinical presentation of UTI may be as follows:
  - Asymptomatic bacteriuria:
    - Presence of bacteriuria ($>10^5$/mL on two occasions in women and on one occasion in men) indicating UTI but without symptoms.
    - Commonly seen in pregnancy.
  - Symptomatic:
    - Acute urethritis, cystitis.
    - Acute prostatitis.
    - Acute pyelonephritis.
    - Septicaemia with septic shock.

Aetiology

- Common microorganisms involved in UTIs are *Escherichia coli* (80% cases), *Proteus, Klebsiella, Enterobacter, Pseudomonas, Serratia, Chlamydia trachomatis* and *Neisseria gonorrhoeae* (sexually transmitted).
- About one-third of females with dysuria and frequency have either insignificant number of bacteria in midstream cultures or completely sterile cultures. This subset of patients has been defined as having acute urethral syndrome. The syndrome is often due to infection with usual organisms (where culture reveals only 10^2–10^4 bacteria) or with unusual organisms (*N. gonorrhoeae, Chlamydia trachomatis*).

Pathogenesis

- Bacteria gain access to the bladder via the urethra in the vast majority of cases. Ascent of bacteria from the bladder may then follow, which results in parenchymal infections.
- Females are more prone to the development of cystitis due to several reasons:
  - Short urethra (4 cm).
  - Gram-negative enteric organisms residing near the anal region colonise the periurethral region.
  - Absence of bactericidal prostatic secretions.
  - Sexual intercourse facilitates entry of introital bacteria into the bladder.
- Susceptibility factor—i.e. the uroepithelium of these patients has more surface receptors to which adherent strains of *E. coli* become attached.
- Whether bladder infection ensures depends on certain factors.
  - Flushing and dilutional effects of micturition and voiding.
  - Direct antibacterial properties of urine and the bladder mucosa.
  - Size of inoculum.
  - Bacterial virulence factors.
- There are a number of other factors involved in the pathogenesis of UTI.
  - Pregnancy is associated with an increased incidence of UTI. During pregnancy ureteral tone is decreased (progestational activity), ureteral peristalsis is decreased and there is a transient incompetence of the vesicoureteral valves. All these factors favour the development of UTI.
  - Any impediment to the free flow of urine as with tumours, strictures, calculi, prostatic hypertrophy and posterior urethral valves favour the development of UTI.
  - Instrumentation of urinary tract like catheterization, urethral dilatation and cystoscopy.
  - Vesicoureteric reflux. This condition in defined as reflux of urine from the bladder cavity up into the ureters. It occurs during voiding or with elevated bladder pressure. As a fluid connection exists between the bladder and kidney, there is retrograde bacterial spread resulting in acute pyelonephritis. Vesicoureteric reflux can be confirmed radiographically when retrograde movement of radiopaque material can be demonstrated (micturating cystourethrography—MCU).

- Associated disorders that impair defence mechanisms like diabetes mellitus favour the development of UTI.
- Neurogenic bladder dysfunction that occurs with spinal cord injuries, tabes dorsalis and multiple sclerosis also predisposes to UTI.

Clinical Features

- Fever with chills and rigors
- Frequency of micturition
- Dysuria or scalding micturition
- Urgency
- Haematuria
- Suprapubic pain resulting from cystitis
- Strangury results from cystitis. After the bladder has been emptied there may be an intense desire to pass more urine due to detrusor spasm
- Urine is cloudy with an unpleasant odour.

Uncomplicated Urinary Tract Infection

- Includes cystitis or urethritis due to bacterial colonisation of the bladder or urethra.
- Affects females much more than males.
- Characterised by burning on urination and frequent urination without fever or flank pain.
- Rare Sequelae.

Complicated Urinary Tract Infection

- Infection whether localized to the lower or upper tract, and associated with an underlying condition that increases the risk of failing therapy is called complicated infection, It often involves renal parenchyma (pyelonephritis) or prostate (prostatitis).
- Infections in men are often considered complicated.
- May be difficult to treat with relapses after treatment common.
- Sequelae like sepsis, metastatic abscesses and renal failure are common.

Underlying Conditions in Complicated Urinary Tract Infections

- Diabetes	- Presence of an indwelling urethral catheter, stent, nephrostomy tube
- Pregnancy	- Recent urinary tract instrumentation
- Hospital acquired infection	- Functional or anatomic abnormality of the urinary tract
- Renal failure	- Immunosuppressed patient
- Urinary tract obstruction	

Investigations

- Dip stick tests are often used to detect nitrite (a metabolic product of typical pathogens of the urinary tract) and leucocyte esterase (a marker of inflammation). Presence of either of them increases the possibility of UTI.
- A freshly voided midstream urine specimen obtained by a "clean-catch" technique should be examined for leucocytes, leucocyte casts and red cells. Suprapubic aspiration of bladder avoids a contaminated urine sample but is rarely required.
- Gram staining and bacterial colony count.
- Culture and sensitivity.

Special Investigations

- Rectal examination to assess the prostate.
- Prostatic massage followed by urine culture if suspicion of prostatitis.
- Cystoscopy in suspected bladder lesions.
- Renal ultrasonography to identify obstruction, cysts and calculi.
- Intravenous urography (IVU), including a post-void film of bladder to identify physiological and anatomical abnormalities of urinary tract.
- MCU to identify and quantitate vesicoureteric reflux and disturbed bladder emptying.
- Dimercaptosuccinic acid (DMSA) renal scan for pyelonephritis.

- In females with recurrent UTI, pelvic examination is mandatory to exclude cystocele, rectocele and uterovaginal prolapse.

Causes of Sterile Pyuria

• Partially treated UTI	• Bladder tumours
• Calculi in urinary tract	• Chemical cystitis
• Urinary tuberculosis	• Prostatitis
• Infection with other organisms (e.g. *Chlamydia*, *Corynebacterium*, etc.)	• Interstitial nephritis
	• Appendicitis

Treatment

- Fluid intake more than 2 L/day to initiate water diuresis, so as to maintain a high rate of urine flow.
- If patient has a stone, catheter or other obstructions, no antibiotics unless symptomatic.
- Regular complete bladder emptying.
- Alkalinisation of urine.
- Urinary analgesics and antispasmodics for detrusor spasm.
- Antibiotic therapy. The choice of antibiotic depends on the organism isolated. The commonly employed antibiotics include cotrimoxazole, ampicillin, amoxicillin, cephalosporins, nitrofurantoin and quinolones. Aminoglycosides should be used for gram-negative infections. Chlamydial infection is treated with tetracycline 500 mg QID. Antibiotics are given for a period of 3 days in uncomplicated infections (nitrofurantoin for 7 days) and for 7–10 days in complicated infections. For complicated infection, parenteral antibiotics preferable to oral ones.
- In females, maintenance of adequate perineal hygiene, emptying the bladder before and after intercourse, and application of 0.5% cetrimide cream to periurethral area before intercourse reduces the incidence of UTIs.
- Double micturition is to be practised if reflux is present.
- Asymptomatic bacteriuria should be treated if a patient: is pregnant, is a case of renal transplantation or is being planned for a urologic surgery. Treatment of asymptomatic bacteriuria in pregnant women decreases the occurrence of pyelonephritis which may also cause damage to the child. Treatment is not required in premenopausal, nonpregnant women, diabetic patients, elderly, or patients with spinal cord injury or indwelling urethral catheters.

Q. Discuss the clinical features, investigations and management of acute pyelonephritis.

- Acute pyelonephritis is an infection of the upper urinary tract. The renal pelvis is acutely inflamed and there is often coincident cystitis. Small cortical abscesses and linear streaks of pus in the medulla may be present.
- Progression of upper urinary tract infection to emphysematous pyelonephritis, renal abscesses, perinephric abscess, or papillary necrosis indicates complicated acute pyelonephritis.

Clinical Features

- There is commonly sudden onset of pain in one or both loins, radiating to the iliac fossa and suprapubic area.
- Frequent passage of small amount of scalding, cloudy urine may be a symptom.
- Fever with chills and rigors may occur.
- Tenderness and guarding are usually present in the renal angle.
- In the presence of obstruction (stone, tumour, bladder neck obstruction, enlarged prostate), acute pyelonephritis can be extremely severe and may progress to renal abscess.

Investigations

- Peripheral blood leucocytosis is a characteristic feature.
- Microscopic examination of urine shows numerous pus cells and organisms, some red cells and epithelial cells.
- Culture of MSU may grow the organism.
- Investigations to exclude anatomical abnormalities of the urinary tract are required when the diagnosis is uncertain, patient has severe presentations when obstruction or abscess must be expeditiously excluded, or if there is inadequate response or rapid recurrence following appropriate therapy.
  - Ultrasound studies are used most frequently, but are relatively insensitive.
  - Computerised tomography (CT) is the imaging modality of choice if ultrasound is normal. It will identify calculi, gas, haemorrhage, obstruction, renal enlargement and inflammatory masses.

- IVU is rarely required at present. A radionuclide scan (where the radionuclide agent is injected into bladder through suprapubic route) may be performed to detect reflux.
- DMSA renal scan performed within 2 days can help in diagnosing acute pyelonephritis. However, a scan done 4–6 months after an acute episode is more important to detect renal parenchymal damage in the form of renal scarring.

Management

- In most cases oral cotrimoxazole, ampicillin, amoxicillin and quinolones (ciprofloxacin, norfloxacin), all active against *E. coli,* are effective.
- Severe or septicaemic cases require intravenous ampicillin, amoxicillin plus aminoglycosides, such as tobramycin, or cephalosporin, such as cefuroxime,. or quinolone for 10–21 days.

Q. Give an account of the aetiopathogenesis, clinical features, investigations and management of chronic pyelonephritis (reflux nephropathy).

- Chronic pyelonephritis (also called reflux nephropathy) refers to chronic interstitial nephritis that occurs as a result of recurrent UTIs, commonly due to severe vesicoureteric reflux in children.

Aetiopathogenesis

- Reflux of urine from the bladder into the ureter during voiding is normally prevented because the ureter passes through the vesical wall obliquely, and is therefore occluded during contraction of the bladder. Abnormalities of the intramural ureter allow reflux to occur and organisms from the bladder to reach the kidney.
- Vesicoureteric reflux is commonly congenital, but can be due to obstructive lesions at the bladder neck. It may be unilateral or bilateral. Reflux diminishes as the child grows and usually disappears.
- When UTI occurs in the presence of obstruction or stasis, whatever the cause, permanent renal damage may result in any age group.
- The most important morphological changes in the kidney are the presence of coarse scars. Each scar is associated with contraction of the related papilla and dilatation of the corresponding calyx.

Clinical Features

- Clinical features may include lassitude, vague ill-health, or symptoms of uraemia or hypertension. Other symptoms include frequency of micturition, dysuria and aching lumbar pain. Pyuria may be present.

Investigations

- Culture of the urine is mandatory. *E. coli* is the most common organism. Other agents include *Proteus, Pseudomonas aeruginosa* and staphylococci.
- Ultrasound of kidneys.
- DMSA scan more accurate than IVU in evaluating the presence of renal lesions subsequent to UTI in the face of reflux.
- Intravenous urogram shows the diagnostic features. There is localised contraction of the renal substance associated with clubbing of the adjacent calyces.
- A micturating cystourethrogram (MCU) will disclose vesicoureteric reflux. This has been replaced by radionuclide cystography scan in many centres.
- Cystoscopy and urography may help to identify any abnormality causing obstruction to the flow of urine.

Management

- Attempts should be made to correct abnormalities of the urinary tract, including malformations. Calculi should be removed.
- Appropriate antibiotics should be given for 7 days.
- If the infection cannot be eradicated, suppressive therapy may be required with trimethoprim (100 mg at bedtime) or nitrofurantoin (50 mg at bedtime) for several months.
- Complete emptying of the bladder should be ensured. If reflux is present "double micturition" is practised. The patient is advised to empty the bladder and then again attempt to empty a second time, approximately 10–15 minutes later.
- Control of hypertension is essential.
- Surgery is indicated if the vesicoureteric reflux persists. Most cases of childhood reflux tend to disappear spontaneously.

Q. Write a short note on chronic kidney disease.

- CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health.

Criteria For CKD

- Glomerular filtration rate (GFR) of <60 mL/minute/1.73 m^2 for 3 months or more, with or without kidney damage

  OR

- Kidney damage for 3 or more months with or without decreased glomerular filtration rate (GFR), as evidenced by any of the following:
  - Microalbuminuria (urinary albumin excretion rate 30–300 mg/day or urinary albumin >30 mg/g excretion of creatinine)
  - Macroalbuminuria (urinary albumin excretion rate >300 mg/day)
  - Persistent haematuria (where other causes such as urologic conditions have been excluded)
  - Urine sediment abnormalities
  - Electrolyte abnormalities due to tubular disorders
  - Pathologic abnormalities (e.g. abnormal renal biopsy)
  - Radiologic abnormalities (e.g. scarring or polycystic kidneys on renal ultrasound scan)
  - History of renal transplantation

Progression

- Major outcomes of CKD include progression to kidney failure, complications from decreased kidney function and development of cardiovascular disease.
- Cardiovascular events are more common than renal failure.
- Because of the older age at onset for many forms of CKD and the slow rate of decline in kidney function, decreased kidney function is far more common than kidney failure.
- Kidney failure is defined as a GFR <15 mL/minute/1.73 m^2, usually accompanied by signs and symptoms of uraemia, or as the need for initiation of kidney replacement therapy (dialysis or transplantation) for management of the complications of a decreased GFR [the term "end-stage renal disease" (ESRD) is used when renal replacement therapy is required].
- Therapeutic interventions in the earlier stages may prevent or reduce some of these complications including progression to kidney failure.

Stages

- CKD is classified based on its cause, GFR category, and albuminuria category

GFR category	Description	GFR (mL/minute/1.73 m^2)
G1	Slight kidney damage with normal or increased filtration	>90
G2	Mild decrease in kidney function	60–89
G3	Moderate decrease in kidney function	30–59
G4	Severe decrease in kidney function	15–29
G5	Kidney failure (often requires dialysis or transplantation)	<15

Albuminuria category	Description	Albuminuria (mg/24 hours)	Albumin to creatinine ratio (mg/g)
A1	Normal to mildly increased	<30	<30
A2	Moderately increased	30–300	30–300
A3	Severely increased	>300	>300

Risk Factors for Developing CKD

Factors	Examples
• Increased susceptibility to kidney damage	Older age, family history of chronic kidney disease (CKD), low birth weight, low income or educational level
• Factors initiating kidney damage	Diabetes mellitus, hypertension, autoimmune diseases, systemic infections, UTIs, urinary stones, obstruction of lower urinary tract, drug toxicity
• Worsening kidney damage	Higher level of proteinuria, higher blood pressure level, poor glycaemic control in diabetes, smoking
• Increased morbidity and mortality in kidney failure	Anaemia, low serum albumin level, late referral for dialysis

- Patients with GFR category of G1 or G2 along with albuminuria category of A1 have low risk of progression of CKD.

Evaluation

- Evaluation to determine:
  - Specific diagnosis.
  - Reversible causes.
  - Co-morbid conditions.
  - Disease severity as assessed by the level of kidney function.
  - Complications due to fall in kidney function.
  - Risk for loss of kidney function.
  - Risk for development of cardiovascular disease.

Treatment

- Therapy for reversible causes.
- Therapy for the underlying cause of kidney disease.
- Therapy for the associated co-morbid conditions.
- Review of all medications including drug-drug interactions as well as potential adverse effect on kidney function or complications. Avoid exposure to gadolinium contrast in patients with CKD stages 4 and 5 because it increases risk for nephrogenic systemic fibrosis.
- DASH diet (Dietary Approaches to Stop Hypertension), which is high in fruits, vegetables, and dairy foods containing little total saturated fat and cholesterol. However, DASH diet is only recommended for patients with a GFR >60 mL/min/1.73 m^2 (stage 1 or 2 CKD) because it contains more protein, potassium and phosphorous than recommended for patients with stage 3 or 4 CKD. For stage 4 and 5, low protein diet of 0.6 g/kg body weight is recommended.
- Measures to slow loss of kidney function.
  - Control of blood pressure (below 140/90 mmHg) using ACE inhibitors or angiotensin receptor blockers in CKD with or without diabetes. In non-diabetics without CKD (without proteinuria), ACE inhibitors, ARBs, calcium channel blockers or thiazides (in non-black).
  - Use of ACE inhibitors (or angiotensin receptor blocker if ACE inhibitors are not tolerated) to reduce proteinuria.
  - Addition of diltiazem, verapamil, thiazides or furosemide to further reduce proteinuria.
  - Control of diabetes (HbA$_1$c ~ 7.0).
  - Lowering of salt intake to below 2 g of sodium/day (equivalent to <5 g of common salt/day).
  - Use of lipid-lowering agents.
  - Cessation of smoking.
  - Weight reduction.
- Measures to prevent and treat cardiovascular disease.
- Measures to prevent and treat complications of decreased kidney function
  - In the absence of suspected or documented deficiency of vitamin D, routine supplementation to suppress elevated PTH concentrations is not recommended.
  - Oral bicarbonate therapy if serum bicarbonate concentrations <22 mEq/L.

- Preparation for kidney replacement therapy.
- Replacement of kidney function by dialysis or transplantation.

Q. Discuss the aetiology, clinical features, investigations, diagnosis and management of chronic renal failure (CRF).

Q. Describe renal osteodystrophy.

- Chronic renal failure (CRF) is defined as irreversible deterioration in renal function over 3 months with GFR <15/minute/1.73 m^2.

Causes

• Primary or secondary glomerulonephritis	• Analgesic nephropathy
• Diabetic nephropathy	• Vesicoureteric reflux
• Hypertensive nephrosclerosis	• Renal tuberculosis
• Polycystic kidney disease	• Nephrocalcinosis
• Chronic pyelonephritis	• Obstructive uropathy
• Tubulo-interstitial diseases	

Clinical Features

- Anorexia, nausea and vomiting are usually attributed to the formation of ammonia from urea in the upper gastrointestinal tract.
- Anaemia in CRF is normochromic and normocytic in type, and is primarily due to reduced erythropoietin production by the kidney. The causes of anaemia in CRF are given in the information box.

Causes of anaemia in CRF

• Decreased erythropoiesis due to reduced availability of erythropoietin	• Uraemic toxin depression on marrow precursor cells
• Reduced dietary intake due to anorexia	• Reduced red cell survival
• Impaired intestinal iron absorption and reduced iron mobilisation from body stores (due to increased hepcidin)	• Increased blood loss due to poor platelet function and capillary fragility
• Anaemia of chronic disease	

- The term renal osteodystrophy embraces various forms of bone disease that develop in CRF. Renal osteodystrophy includes osteomalacia, hyperparathyroid bone disease (osteitis fibrosa), osteoporosis and osteosclerosis. Osteomalacia results from the failure of the kidney to produce 1,25-dihydroxycholecalciferol, which causes decreased intestinal absorption of calcium. This leads to reduction in calcification of bone. The low plasma calcium stimulates the parathyroid gland resulting in secondary hyperparathyroidism. In some patients tertiary autonomous hyperparathyroidism develops. Osteoporosis is probably related to malnutrition. Osteosclerosis literally means "hardening of bone", and may be a direct result of excess parathyroid hormone. Alternate bands of sclerotic and porotic bone in the vertebrae produce the characteristic "rugger jersey spine" in the radiograph.
- Generalised myopathy is due to a combination of poor nutrition, hyperparathyroidism and vitamin D deficiency.
- Neuropathy may be motor, sensory or autonomic.
- Endocrine abnormalities include amenorrhoea in females and loss of libido in both sexes.
- Pericarditis is a common cardiovascular complication in untreated end-stage renal failure.
- Hypertension develops in approximately 80% of patients with CRF.
- Metabolic acidosis is a common accompaniment of CRF.
- Electrolyte abnormalities particularly hyperkalaemia, hypocalcaemia and hyperphosphataemia.
- Patients with CRF have increased susceptibility to infections due to impaired cellular and humoral immunity.
- In addition, uraemia can affect the lung ("uraemic lung") and brain ("uraemic encephalopathy").
- Frequently patients complain of pruritus, often intractable.
- Dialysis dementia and dialysis disequilibrium are dialysis-related complications.

ANAEMIA
Pallor
Lethargy
Breathlessness

PLATELET ABNORMALITY
Epistaxis
Bruising

SKIN
Pigmentation
Pruritus

GI TRACT
Anorexia
Nausea, vomiting
Diarrhoea

ENDOCRINE/GONADS
Amenorrhoea
Erectile impotence
Infertility
Peripheral neuropathy

CNS
Confusion
Coma
Fits

CVS
Uraemia pericarditis
Hypertension
Peripheral vascular disease
Heart failure

RENAL
Nocturia
Polyuria

RENAL OSTEODYSTROPHY
Osteomalacia
Muscle weakness
Bone pain
Hyperparathyroidism
Osteosclerosis

Oedema

Signs and symptoms of CRF

Investigations

- Important urinary abnormalities include a fixed specific gravity around 1.010 (isosthenuria) and the presence of broad casts.
- White cells in the urine usually indicate infection but may also occur in renal tuberculosis and papillary necrosis.
- Eosinophils in the urine indicate allergic tubule-interstitial disease while red cell casts suggest glomerulonephritis.
- The common haematological abnormality is a normochromic normocytic anaemia.
- The most consistent biochemical abnormalities are elevated levels of blood urea and creatinine. The level of serum creatinine correlates with the degree of renal impairment. Other biochemical abnormalities include hypocalcaemia, hyperphosphataemia, hyperuricaemia and hyperkalaemia. Bicarbonate levels are reduced.
- Creatinine clearance is important to assess the severity of renal failure.
- A plain radiograph of the abdomen may be useful in determining the kidney size and in the evaluation of obstructive uropathy.
- Renal ultrasound typically shows shrunken kidneys. In diabetic glomerulosclerosis, amyloidosis, polycystic kidney diseases, bilateral hydronephrosis and myeloma kidney, the kidneys may be of normal size.
- CT is useful in some patients with suspected obstructive nephropathy.
- Transcutaneous renal biopsy is of value in establishing the diagnosis in selected cases, particularly in cases associated with normal-sized kidneys, with the possible exception of diabetic glomerulosclerosis. It is particularly useful if renal functions are deteriorating rapidly.

Management

- Refer also to CKD above.
- The management of CRF falls into three parts:
  - Investigations to determine the nature of underlying disease and to detect any reversible factors.
  - Measures to prevent further renal damage.
  - Supportive measures in the form of dialysis or transplantation when required.
- Some of the reversible factors in CRF which require treatment are:

- Hypertension	- Septic shock
- Urinary tract infection (UTI)	- Cardiogenic shock
- Urinary tract obstruction	- Infections
- Haemorrhage	- Nephrotoxic drugs

- The following measures can be undertaken which will reduce the symptoms and may slow the progression to terminal renal failure.
  - Control of hypertension: The blood pressure should be reduced to less than 140/90 mmHg. If creatinine is below 3 mg/dL, ACE inhibitors are the drugs of choice.
  - Protein restriction to 40 g/day (with higher amount of essential amino acids).
  - Avoidance of high potassium foods.
  - Salt restriction is required in most cases. However, patients with salt-losing nephropathy (tubulo-interstitial disease) require a high-salt intake.
  - Hypocalcaemia and hyperphosphataemia should be treated aggressively. Hypocalcaemia requires treatment with calcitriol or alphacalcidol (1-α-hydroxyvitamin D_3) or paricalcitol (19-nor-1,25-dihydroxyvitamin D_3) and calcium supplementation. Vitamin D supplementation reduces cardiovascular mortality in ESRD patients. Serum calcium should be monitored frequently to avoid hypercalcaemia. Oral calcium carbonate also reduces the bioavailability of dietary phosphates.
  - Phosphate binders:
    - Previously, aluminium hydroxide was used to bind phosphates in the gut. However, aluminium toxicity was common in these patients.
    - Calcium carbonate and calcium acetate; serum calcium should be monitored.
    - Sevelamer carbonate, an anion-exchange resin.
    - Lanthanum carbonate, a non-aluminium, non-calcium phosphate-binding agent (higher incidence of side effects).
  - Treating hyperparathyroidism:
    - Use of calcium carbonate or acetate.
    - Use of vitamin D analogues.
    - Use of calcimimetics sensitised calcium receptor to serum calcium on parathyroid cells, resulting in fall of PTH secretion. Cinacalcet has been approved for use in patients on dialysis.
  - Metabolic acidosis should be corrected with calcium carbonate, and if required, with small doses of sodium bicarbonate.
  - Hyperkalaemia usually responds to dietary restrictions. Some patients require addition of potassium-exchange resins.
  - Anaemia should be corrected by appropriate addition of iron, folate and vitamin B_{12}, if required. The treatment of choice for renal failure-associated anaemia is the use of erythropoietin along with iron. Blood pressure should be carefully monitored during erythropoietin therapy. Oral or intravenous iron is needed to maintain adequate iron stores (transferrin saturation >20% and serum ferritin levels >100 ng/mL). Target haemoglobin is 11–12 g/dL. Haemoglobin >13 g/dL has been shown to be associated with increased incidence of cardiovascular mortality.
- If conservative measures are inadequate, haemodialysis may be needed.
- Kidney transplantation offers the possibility of restoring normal kidney functions.
- Indications for urgent dialysis:
  - Severe hyperkalaemia
  - Pulmonary oedema or severe fluid overload
  - Severe metabolic acidosis
  - Uraemic pericarditis
  - Uraemic encephalopathy
  - Toxicity with a dialyzable poison (methanol, phenobarbital).

Q. What are the renal replacement therapies available?

Renal Replacement Therapies

- Dialysis	- Clearance of small molecules and toxins using diffusion across a membrane
- Haemodialysis	- Dialysis with clearance across a synthetic membrane
- Peritoneal dialysis	- Dialysis with clearance across a native membrane
- Ultrafiltration	- Fluid removal across a semipermeable membrane during dialysis by convection (solutes are moved under pressure across a membrane)
- Haemofiltration	- Continuous dialysis therapy in which large amounts of fluid are removed from blood by convection with concurrent reinfusion of an electrolytic solution
- Haemodiafiltration	- Combination of haemodialysis and haemofiltration
- Continuous renal replacement therapies	- Include haemofiltration and haemodiafiltration

Q. Write a note on haemodialysis.

- In principle, haemodialysis allows accumulated uraemic toxins (e.g. urea and creatinine) and electrolytes (e.g. potassium) to diffuse across a semipermeable membrane from the blood, where they are in high concentrations, to the dialysate fluid on the other side of the membrane.
- Blood is circulated through an artificial kidney. The artificial kidney consists of a blood compartment and a dialysis fluid compartment, separated by a semipermeable membrane. As the blood and the dialysis fluid move on either side of the membrane, diffusion of electrolytes and small molecular weight substances occur.
- The dialyser membrane can be made up of four types of materials: cellulose, cellulose acetate, cellulosynthetic and synthetic (polysulphone, polyacrylonitrile). Synthetic membrane is preferred as it causes very little complement activation.
- Each session of haemodialysis usually lasts for 4–5 hours. Two or three sittings per week may be necessary.
- For long-term dialysis access to the bloodstream is ensured by the creation of an arteriovenous fistula, usually in the forearm. Another option is by interposing a piece of synthetic material between native artery and native vein (graft).

Complications

- The major complication is hypotension during dialysis. Factors that contribute to hypotension include:
  - Excessive removal of extracellular fluid.
  - Shift of fluid into intracellular compartment due to rapid reduction in urea in the extracellular compartment.
  - Abnormalities of venous tone.
  - Autonomic neuropathy.
  - Acetate toxicity that causes vasodilatation.
- Other complications include muscle cramps, anaphylactoid reaction to the dialyser, air embolism, infections, haemolysis and pulmonary oedema.
- Dialysis disequilibrium syndrome occurs following a dialysis session, and is characterised by nausea, vomiting, restlessness, headache, hypertension, myoclonic jerks and in severe case, seizures and coma. This is due to rapid changes in plasma osmolality that produces cerebral oedema. Management is supportive.
- Patients on long-term haemodialysis may develop dialysis dementia. It is characterised by speech dyspraxia, myoclonic jerks, dementia, seizures and later, death. Aluminium toxicity is the most important factor in the pathogenesis of this disorder. Some viral infection may also play a role in this.
- The rate of death from cardiac disease is higher in patients on haemodialysis as compared to patients on peritoneal dialysis or after renal transplantation.
- Other complications seen in patients on dialysis include Wernicke's encephalopathy and central pontine myelinolysis (due to rapid correction of hyponatraemia).

Acute Dialysis in Critically Ill Patients

- Continuous renal replacement therapy (CRRT) modalities are used in critically ill patients who are unable to tolerate large fluid shifts and hypotension that frequently accompany standard haemodialysis.
- Allows slow and isotonic fluid removal, resulting in excellent haemodynamic tolerance, even in patients with shock or severe fluid overload.
- Since dialysis is continuous, volume removal and correction of metabolic abnormalities can be modified at any time, allowing for rapid adjustments in critically ill patients.
- Several CRRT modalities are available. The most common is continuous veno-venous haemodiafiltration, which combines convective and diffusive clearance through a dialyser with reinfusion of electrolyte-rich solutions.
- CRRT is the dialysis modality of choice in patients with ARF combined with haemodynamic instability, cerebral oedema, severe fluid overload and hepatic encephalopathy.
- Complications include embolisation, arteriovenous fistula formation, haemorrhage and infection from catheter access.

Q. Write a short note on peritoneal dialysis.

- In peritoneal dialysis, the peritoneum of the patient acts as a semipermeable membrane across which diffusion of water and solutes takes place.
- A plastic or silicone catheter is placed into the peritoneal cavity through the anterior abdominal wall. Dialysate (2 L) is instilled into the peritoneal space. Water, urea, creatinine and other toxins pass across the peritoneal membrane into the dialysate. The fluid is removed by gravity after 30–60 minutes, and the same procedure is repeated several times. This is called intermittent peritoneal dialysis. It is chiefly used in ARF.

- The main complication is the occurrence of peritonitis and infections around the catheter site. Some patients may develop pleural effusion.
- There are other forms of peritoneal dialysis that are useful for chronic dialysis.

Continuous Ambulatory Peritoneal Dialysis (CAPD)

- Here, the dwelling time of fluid is long so that only three to five cycles are done in a day. The patient infuses 1.5–3 L of dialysate in the peritoneal cavity. The solution is allowed to remain for more than 4 hours during the day and 8–12 hours at night. This technique is useful for maintenance of dialysis in patients with CRF.

Continuous Cycling Peritoneal Dialysis (CCPD)

- Here, the dwelling period is longer than CAPD during the daytime but at night time an automated cycler performs short exchanges.

Q. Write a short note on renal transplantation.

- Successful renal transplantation offers the potential for complete rehabilitation in advanced CRF.
- The donor is most often a living related person.
- Living donors should be healthy with the same ABO blood group as the recipient. He/she should be free of hypertension, diabetes, or malignant disease (except possibly those with neoplasms originating in the CNS).
- The donor's HLA is matched with that of the recipient. It is preferable to have a HLA-identical donor. Class I antigens (HLA-A, -B and -C) are detected by a lymphocyte assay and class II (HLA-DR) by mixed lymphocyte culture. If an HLA-identical donor is not available, haplo-identical (half-identical) living donor is required for long survival of the graft.
- Pre-sensitisation (presence of antibodies against donor ABO and class I antigens) is detected by a cross-match, which if positive is a contraindication for transplantation.
- With the acceptance of the concept of brain death in India, an increasing number of cadaveric transplants are being performed at present.

Contraindications

Absolute contraindications	Relative contraindications
- Reversible renal involvement - Disseminated or untreated cancer - Severe psychiatric disease - Persistent substance abuse - Severe mental retardation - Un-reconstructable coronary artery disease - Refractory congestive heart failure - Active infection - Active glomerulonephritis - Previous sensitisation to donor tissue	- Iliofemoral occlusive disease - Diabetes mellitus - Severe bladder or urethral abnormalities - Elderly age group - Chronic liver disease - Treated malignancy

Surgical Procedure

- The recipient receives a haemodialysis before transplantation to ensure a relatively normal metabolic state.
- In a transplant operation, the donor kidney is placed in an extraperitoneal pouch in the iliac fossa of the recipient. The renal artery and vein are anastomosed to the recipient's iliac vessels. The donor ureter is implanted into the bladder.
- The recipient's own kidneys are left undisturbed.

Immunosuppressive Therapy

- Current immunosuppressive therapy varies from centre to centre. A combination of drugs is often used to prevent rejection.
- Commonly used immunosuppressants include steroids, calcineurin inhibitors (e.g. cyclosporin, tacrolimus), antiproliferative agents (e.g. azathioprine, mycophenolate mofetil) and antilymphocyte or antithymocyte globulin. Newer drugs include basiliximab and daclizumab (antibodies against interleukin-2 receptor).

Complications

- Despite prophylaxis with immunosuppressants begun just before or at the time of transplantation, most recipients undergo one or more rejection episodes.
- Hyperacute rejection
  - A complement-mediated response in recipients with pre-existing antibodies to the donor (for example, anti-ABO blood type antibodies). Complement activation within the graft is followed by endothelial necrosis, platelet deposition and local coagulation.
  - Occurs within minutes, and the transplant must be immediately removed to prevent a severe systemic inflammatory response and generalised clotting.
- Acute rejection
  - Mediated by T cells; sometimes also by antibodies.
  - Acute rejection is suggested by deterioration of renal function, hypertension, weight gain, tenderness and swelling of the graft, fever, and appearance in the urine sediment of protein, lymphocytes and renal tubular cells.
  - If the diagnosis is unclear, percutaneous needle biopsy is performed for histopathologic evaluation of tissue.
  - Treatment of acute rejection involves the use of additional immunosuppressants including intravenous pulses of methylprednisolone and antilymphocyte antibody.
  - Antibody-mediated rejection is less likely to respond to steroids and can be treated with plasma exchange (to remove the antibody) and intravenous immunoglobulin.
- Chronic rejection
  - Some patients suffer irreversible chronic graft rejection.
- Other complications
  - Drug toxicity including adverse effects of prednisolone.
  - Infections.
  - Recurrent underlying renal disease (e.g. hyperoxaluria).
  - In addition, the incidence of malignancy in renal allograft recipients is increased.

Q. Discuss briefly the pathogenesis, clinical features, investigations and management of acute renal failure.

Q. Give a brief account of acute kidney injury.

Definition

- Acute renal failure (ARF) is defined as a rapid, potentially reversible deterioration in renal function sufficient to result in accumulation of nitrogenous wastes in the body (uraemia):
  - An increase in serum creatinine of ≥ 0.3 mg/dL within 48 hours; or
  - An increase in serum creatinine of ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior seven days; or
  - Urine volume <0.5 mL/kg per hour for more than six hours.
- Presently, the term acute kidney injury (AKI) is often used in place of ARF. The conventionally used term ARF is often used in reference to the subset of patients with a need for acute dialysis support.
- RIFLE criteria are used to classify severity of AKI. The acronym RIFLE stands for the increasing severity classes— Risk, Injury and Failure, and the two outcome classes—Loss and End-stage kidney disease. The three severity grades are defined on the basis of changes in serum creatinine or urine output where the worst of each criterion is used. Also, two outcome criteria are defined by duration of loss of kidney function, 4 weeks and 3 months, respectively.

Criteria	Definition
• Risk	Increased creatinine × 1.5 times OR Urine output <0.5 mL/kg/hour × 6 hours
• Injury	Increased creatinine × 2 times OR Urine output <0.5 mL/kg/hour × 12 hours
• Failure	Increased creatinine × 3 times or creatinine ≥ 4 mg/dL (acute rise of ≥ 0.5 mg/dL) OR Urine output <0.3 mL/kg/hour × 24 hours OR Anuria × 12 hours

| • Loss | Persistent AKI = complete loss of renal function >4 weeks |
| • End-stage kidney disease | End-stage kidney disease (>3 months) |

- As per Acute Kidney Injury Network (AKIN) classification, AKI is classified into three stages.
  - Stage 1 is same as Risk category of RIFLE with addition of increase in serum creatinine by 0.3 mg/dL.
  - Stages 2 and 3 are same as Injury and Failure categories of RIFLE.

Aetiopathogenesis

- The kidneys receive approximately 25% of the cardiac output at rest.
- In pre-renal ARF the kidneys are inadequately perfused (due to diminished cardiac output), and the GFR is greatly diminished resulting in oliguria (urine output <400 mL/day).
- Renal causes of ARF result from intrinsic diseases of the kidneys themselves, namely glomerular, tubulo-interstitial or vascular diseases. In acute tubular necrosis (ATN), a diminution in the supply of oxygen and nutrients to the tubular cells result in ischaemia and necrosis of the tubular cells. Fortunately, the tubular cells can regenerate when the causative factors are removed.
- Post-renal ARF is caused by obstruction of the urinary tract at any point in its course.

Causes

Prerenal causes	
• Hypovolaemia	Haemorrhage, severe vomiting, diarrhoea, loss of plasma as in burns, pancreatitis, excess of diuretics, diabetic ketoacidosis
• Reduced cardiac output	Heart failure, septic shock
• Renal vessel diseases	Renal artery obstruction
• Drugs	ACE inhibitors, NSAIDs
Renal causes	
• Glomerular diseases	Glomerulonephritis (rapidly progressive GN, acute GN, others)
• Vascular diseases	Vasculitis, renal artery occlusion
• Acute tubulo-interstitial nephritis	Drugs (cephalosporins, sulphonamides, NSAIDs, rifampicin), infections
• ATN	Renal ischaemia due to any cause, transfusion reactions, malaria, (rhabdomyolysis) crush injury, heavy metals, septic abortion, drugs (contrast agents, aminoglycosides)
Post-renal causes	
• Extrarenal obstruction	Prostatic enlargement, urethral stenosis, tumours, calculi
• Intrarenal obstruction	Uric acid crystals, sloughed papillae

Clinical Features

- In ARF due to a pre-renal disorder the clinical features are those of the causal condition together with those of rapidly developing uraemia. Patients often present with a low blood pressure, poor peripheral perfusion and a falling urine output.
- ATN is the most important cause of ARF due to intrinsic renal disease. The clinical course in ATN can be divided into an oliguric phase, maintenance phase and a diuretic phase.
  - In the oliguric phase, the patient may develop symptoms due to fluid overload and azotaemia. Fluid overload causes elevated jugular venous pressure, pedal oedema, ascites and pulmonary oedema. Hyperkalaemia occurs commonly during this phase. The oliguric phase usually lasts an average of 10–14 days, but may vary from a few hours to as long as 4 weeks.
  - In the maintenance phase, which lasts for days to weeks, the GFR reaches its nadir and the urine output remains low.
  - With the onset of the diuretic phase the urine output progressively increases. In a few days the patient develops polyuria. During this phase the tubular concentrating capacity is defective, and uncontrolled loss of water and electrolytes may lead to dehydration, hyponatraemia and hypokalaemia. Eventually, the renal concentration capacity improves and urine volume decreases to normal.
- Not all patients with ATN develop oliguric failure. As many as 40% of the patients may have normal urine output. This is called non-oliguric renal failure. The electrolyte disturbances are less in these patients.
- Patients with glomerulonephritis typically have hypertension, proteinuria and haematuria.
- Patients with drug-induced acute tubulo-interstitial nephritis may present with fever, skin rash and arthralgias.

- ARF due to bilateral post-renal obstruction commonly causes anuria. The patient may give a history of loin pain, haematuria, renal colic or difficulty in micturition.
- Patients with ARF due to any cause may also have symptoms related to uraemia. These include anorexia, nausea, vomiting, pruritus, mental state changes, seizures and dyspnoea due to fluid overload. Important physical findings include asterixis, myoclonus, pericardial rub, and evidence of fluid overload in the form of oedema, elevated JVP and crepitations.
- Presence of anuria (urine <100 mL/day) indicates obstructive uropathy, bilateral renal cortical necrosis, RPGN (some cases) and acute bilateral renal artery or vein occlusion.

Investigations

Creatinine

- Elevated blood urea and creatinine levels are the most consistent findings. In pre-renal ARF, there is a disproportionate elevation of urea in relation to creatinine.
- However, rise in creatinine is unreliable indicator of early renal injury due to several reasons:
  - Normal serum creatinine is influenced by several non-renal factors such as age, gender, muscle mass, medications, hydration status, nutrition status and tubular secretion.
  - Greater than 50% of kidney function must be lost before serum creatinine rises.
  - It does not reflect true GFR as several hours to days must elapse before a new equilibrium between presumably steady state production and decreased excretion of creatinine is established.
- Therefore, several interventions which can prevent and/or treat early AKI cannot be instituted if diagnosis is solely based on creatinine levels.

Newer Markers

- Novel biomarkers for AKI that can diagnose early cases. These include neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), interleukin 18 (IL-18) and cystatin C.

Other Investigations

- Other biochemical abnormalities include hyperkalaemia, hypocalcaemia, hyperphosphataemia and hyperuricaemia.
- Urine analysis may show red cells, red cell casts and proteinuria in glomerulonephritis. In ATN, urinalysis shows epithelial cells and coarsely granular casts with mild proteinuria.
- In allergic interstitial nephritis, the urine shows white cells, red cells and eosinophils.
- In acute tubulo-interstitial nephritis, proteinuria, glycosuria, aminoaciduria and potassium wasting can occur due to tubular dysfunction.
- Electrocardiogram may reveal evidences of hyperkalaemia.
- Chest radiograph may show evidences of pulmonary oedema and pleural effusion.
- Pre-renal ARF characteristically shows a high urine osmolality (>500 mOsm/kg), low urinary sodium (<20 mmol/L) and a high urine creatinine/plasma creatinine ratio (>40).
- In patients suspected to have RPGN, systemic causes like Wegener's granulomatosis must be excluded by appropriate investigations (cANCA). A kidney biopsy is also indicated in these patients.
- Renal imaging by plain abdominal radiography and ultrasonography may be of value in the evaluation of post-renal ARF.

Management

- Therapy for ARF is directed at correcting fluid and electrolyte abnormalities, treating the underlying cause and preventing complications including nutritional deficiencies.
- An attempt should be made to identify the cause of ARF and to correct it, if possible.
- Administer a challenge of fluid intravenously in patients with clinical history consistent with fluid loss (such as vomiting and diarrhoea) and physical examination consistent with hypovolaemia (hypotension and tachycardia).
- Emergency treatment should be started for hyperkalaemia (K^+ >6 mmol/L) to prevent life-threatening complications.
- Acidosis should be treated with intravenous or oral bicarbonate if serum bicarbonate level is <15 mEq/L.
- Drugs such as loop diuretics, mannitol and dopamine have been used to increase urine output and reduce the duration of renal failure but they have been shown to be of no value.
- Patients who present with severe pulmonary oedema usually require haemodialysis.
- After correction of fluid deficit, maintain a daily fluid intake equal to the volume of the urine output plus 400–500 mL to balance the insensible loss.
- Dietary proteins should be restricted to about 40 g/day. Attempts can be made to suppress endogenous protein catabolism to a minimum by giving as much energy as possible in the form of carbohydrates and fats. Salt should also be restricted.

- Nephrotoxic drugs should be avoided.
- Patients with drug-induced acute tubulo-interstitial nephritis usually recover after stopping the offending drug. At times, short course of steroids may help.
- Patients with RPGN are treated with corticosteroids and cyclophosphamide.
- If conservative measures fail, haemodialysis may be required. The usual indications of haemodialysis in ARF are given in the information box.

Indications of haemodialysis

- Symptomatic uraemia with high blood urea
- Serum creatinine >8 mg/dL
- Resistant hyperkalaemia
- Uraemic pericarditis
- Refractory pulmonary oedema
- Severe metabolic acidosis
- Uraemic encephalopathy

Q. Describe renal tubular acidosis (RTA).

- Renal tubular acidosis (RTA) is a medical condition in which kidneys fail to excrete acids leading to accumulation of acid in the body. This leads to normal anion-gap acidosis. The function of kidneys is otherwise normal.
- May occur either due to failure to recover sufficient bicarbonate ions from the filtrate in the proximal tubule or due to insufficient secretion of hydrogen ions into the distal tubule.
- Four types of RTA are:
  - Type 1 RTA or distal tubular RTA.
  - Type 2 RTA or proximal RTA.
  - Type 3 RTA or mixed RTA.
  - Type 4 RTA or hypoaldosteronism hyperkalaemic RTA.

Type 1 RTA

- Most common type of RTA.
- Occurs due to failure of hydrogen ion secretion by distal tubular cells that lead to a failure to acidify the urine to a pH <5.3 despite metabolic acidosis.

Causes

- Hereditary
- Autoimmune diseases particularly Sjögren's syndrome
- Cirrhosis of liver
- Nephrocalcinosis producing damage of cortical collecting duct
- Renal transplantation
- Sickle cell anaemia
- Drugs and toxins, including ifosfamide, toluene, lithium and amphotericin B
- Chronic urinary tract obstruction.

Consequences

- Variable metabolic acidosis.
- Hypokalaemia.
- Urinary calculus causing haematuria and pain.
- Nephrocalcinosis (deposition of calcium in the substance of the kidney).
- Bone demineralisation (causing rickets in children and osteomalacia in adults).

Diagnosis

- Urinary pH >5.3 in presence of systemic acidosis (serum bicarbonate <20 mEq/L).
- In mild cases, oral ammonium chloride test to produce acid load.

Treatment

- Correction of the acidosis with oral sodium bicarbonate or sodium citrate that reverses bone demineralisation.
- Potassium citrate in case of hypokalaemia, stone formation and nephrocalcinosis.

Type 2 RTA

- Caused by a failure of the proximal tubular cells to reabsorb filtered bicarbonate from the urine, leading to urinary bicarbonate wasting and subsequent acidosis.

- Acidosis, less severe than type 1 RTA and urinary pH may be below 5.3.
- Usually associated with a generalised dysfunction of the proximal tubular cells (Fanconi's syndrome) where there is also phosphaturia, glycosuria, aminoaciduria, uricosuria and tubular proteinuria.
- Due to phosphate wasting, bone demineralisation occurs.

Causes

- Cystinosis
- Galactosaemia
- Glycogen storage disease (type I)
- Hereditary fructose intolerance
- Wilson's disease
- Amyloidosis
- Multiple myeloma
- Drugs and toxins such as antiretroviral drugs, aminoglycosides, ifosfamide, lead and cadmium.

Treatment

- As patients have bicarbonate wasting, large doses of bicarbonate are required.
- Potassium supplementation often required as bicarbonate loss potentiates hypokalaemia.

Type 3 RTA

- Previously used to designate a rare and transient mixed type 1 RTA and type 2 RTA. Presently, this term is used to describe a genetic defect in type 2 carbonic anhydrase in both proximal and distal tubular cells, as well in bone.
- Produces:
  - Proximal RTA
  - Distal RTA
  - Osteopetrosis
  - Cerebral calcification and mental impairment.
- Treatment is similar to that for type 1 and type 2 RTAs. There is no treatment for osteopetrosis or cerebral calcification.

Type 4 RTA

- Associated with a mild metabolic acidosis (normal anion gap) due to a reduction in distal tubular ammonium excretion, which is secondary to hypoaldosteronism.
- Measured urinary acidification is normal.

Causes

Primary aldosterone deficiency	Hyporeninaemic hypoaldosteronism	Aldosterone resistance
- Primary adrenal insufficiency - Congenital adrenal hyperplasia - Aldosterone synthase deficiency - Potassium-sparing diuretics	- Renal dysfunction most commonly diabetic nephropathy - HIV infection - ACE inhibitors - NSAIDs - Cyclosporin	- Drugs (amiloride, spironolactone, trimethoprim, pentamidine) - Pseudohypoaldosteronism

Treatment

- Aldosterone deficiency treated with a mineralocorticoid (such as fludrocortisone) as well as possibly a glucocorticoid for cortisol deficiency, if present.
- Hyporeninaemic hypoaldosteronism is amenable to fludrocortisone treatment but the accompanying hypertension and oedema often require a thiazide or loop diuretic. Diuretics are also required to control hyperkalaemia.

Q. Write a short note on polycystic kidney disease.

- There are two types of polycystic kidney disease.
  - The rare infantile polycystic kidney disease is an autosomal recessive disorder, which is usually fatal. It is associated with biliary dysgenesis resulting in congenital hepatic fibrosis, plus intrahepatic bile duct dilatation (Caroli disease).

- The more common adult polycystic kidney disease (APKD) is an autosomal dominant disorder. The cortex and medulla of both kidneys are usually filled with thin-walled, spherical cysts that enlarge and compress intervening renal tissue, thereby interfering with renal function.
- APKD may be associated with hepatic cysts in more than 75% cases (adult hepatorenal polycystic disease).
- APKD is caused by mutations of either PKD1 or PKD2 gene.
- Clinical presentation may be at any age from the second decade. Presenting manifestations include hypertension, acute loin pain and haematuria resulting from haemorrhage into a cyst or renal calculus, vague abdominal discomfort due to increased size of the kidneys, and symptoms of uraemia and UTI (pyelonephritis and renal cyst infection).
- Polycythaemia (due to increased erythropoietin production), mitral valve prolapse and abdominal hernias are common accompaniments.
- Berry aneurysms of the cerebral vessels are common (10–30%) associations, and may result in subarachnoid haemorrhage.
- Physical examination commonly reveals large irregular kidneys.
- Abdominal ultrasound is the investigation of choice. IVU (rarely done) may demonstrate the characteristic "drooping water-lilly sign". MRI is more sensitive than ultrasound to detect small cysts.
- Treatment includes control of hypertension, control of pain, treatment of infection, and renal replacement by dialysis or transplantation, if required.
- Screening of family members helps to detect this condition.

Q. Describe renal tuberculosis.

Q. Briefly outline the clinical features, investigations and treatment of tuberculosis of the urinary tract.

- Tuberculosis of the urinary tract arises as a blood-borne infection from a distant focus.

Types of Tuberculous Kidney

- Tuberculous papillary ulcer
- Cavernous form
- Hydronephrosis
- Pyonephrosis
- Tuberculous perinephric abscess
- Caseous (putty) kidney
- Miliary

Clinical Features

- Males are more affected than females (2:1) and the right kidney is more commonly affected than the left.
- Manifestations include a dull ache in the renal angle, frequency of micturition, constitutional symptoms like fever and weight loss, haematuria and painful micturition in tuberculous cystitis.
- Physical examination may reveal an enlarged palpable kidney and tenderness in the renal angle.
- Tuberculosis can also involve prostate, seminal vesicles, vas deferens and epididymis.

Investigation

- "Sterile pyuria" is characteristic. Though the urine contains pus cells, it fails to grow any organism on routine culture.
- Urine should be examined for tubercle bacilli. Five early morning consecutive samples should be examined, as there is intermittent excretion of tubercle bacilli. Alternatively, a 24-hour urine collection may be examined for acid-fast bacillus (AFB).
- PCR on urine samples for mycobacteria.
- Culture of the urine may grow tubercle bacilli.
- Plain KUB radiograph may show calcification in the renal parenchyma and ureteric calcification.
- IVU may show irregular contour of the kidney, hydrocalyx, displacement of adjacent calyces by the abscess and a small contracted bladder ("systolic or thimble" bladder).
- Ultrasound may show dilated calyces, hydronephrosis, calcification and small abscesses.
- Cystoscopy may reveal the characteristic "golf hole" appearance of the ureteric orifice due to sclerosing periureteritis.
- Chest radiograph should be done routinely to exclude active or previous pulmonary tuberculosis.

Treatment

- Antituberculous chemotherapy is similar to that for pulmonary tuberculosis.
- Surgical treatment may be required in selected cases.

Chapter 17

Diseases Due to Infections

Q. Define pyrexia of unknown origin (PUO). Discuss briefly your approach to a case of PUO or fever of unknown origin.

Definition

- The classic definition of pyrexia of unknown origin (PUO) is a fever of at least 3 weeks' duration with daily temperature elevation above 101°F and remaining undiagnosed after 1 week of intensive study in the hospital.
- However, with the availability of several investigations on outpatient basis and appearance of several immunodeficiency diseases, a new classification of PUO has evolved. Here, PUO is divided into four types:
  - Classic PUO: Fever of at least 3 weeks' duration with temperature recorded as more than 101°F (38.3°C) on several occasions, and the cause is not found despite three outpatient visits or 3 days of hospitalisation or 7 days of "intelligent" ambulatory investigations.
  - Nosocomial PUO: A temperature of more than 38.3°C (101°F) developing on several occasions in a hospitalised patient who is receiving acute care and in whom infection is not manifest or incubating on admission. It is also mandatory that the cause of fever is not found on 3 days of investigations, including at least 2 days' incubation of cultures.
  - Neutropenic PUO: A temperature of more than 38.3°C (101°F) developing on several occasions in a patient whose neutrophil count is below 500/mL or is expected to fall to that level in 1 or 2 days. Again, it is also mandatory that the cause of fever is not found on 3 days of investigations, including at least 2 days' incubation of cultures.
  - HIV-associated PUO: A temperature of more than 38.3°C (101°F) developing on several occasions over a period of more than 4 weeks for outpatients or more than 3 days for hospitalised patients with HIV infection. It is also mandatory that the cause of fever is not found on 3 days of investigations, including at least 2 days' incubation of cultures.

Aetiology

- Patients with classic PUO usually do not have rare diseases, but suffer from common diseases with atypical presentations.
  - 40% cases — Infections
  - 20% cases — Neoplasms (primary or metastatic)
  - 20% cases — Connective tissue diseases
  - 10% cases — Miscellaneous disorders
  - 10% cases — Undiagnosed.

Common causes of prolonged fever

• Infections	Tuberculosis, malaria, typhoid, infective endocarditis, urinary tract infections, intra-renal and perinephric abscesses, pyogenic and amoebic liver abscesses, subphrenic abscess, retroperitoneal abscess, pelvic inflammatory diseases, HIV infection
• Neoplasms	Lymphomas, leukaemias, gastrointestinal malignancies, metastatic tumours of liver, hypernephroma, atrial myxomas
• CT disorders	Systemic lupus erythematosus, rheumatoid arthritis, temporal arteritis, polyarteritis nodosa (PAN)
• Miscellaneous	Drug fevers (sulphonamides, aminoglycosides, penicillins), multiple pulmonary thromboembolism, haemolytic anaemias, thyroiditis, granulomatous hepatitis, cyclic neutropenia
• Psychogenic fevers	Habitual hyperthermia, factitious fever, fabricated fever
• Periodic fevers	Familial Mediterranean fever (polyserositis)

- In neutropenic patients, infections include perianal infections, aspergillosis and candidaemia.
- In nosocomial PUO, causes include catheter infections, urinary tract infections, septic thrombophlebitis and drug fever.
- In HIV patients, tuberculosis and other infections are common.

- In general population a single pathology is the norm, while in HIV patients about 20% have two or more simultaneous causes of PUO.

Diagnostic Approach to PUO

- Most pyrexias of "unknown origin" are atypical or obscure presentations of common diseases rather than due to obscure diseases.
- "There is no substitute for observing the patient, talking to him and thinking about him".
- History should be reviewed with particular emphasis on family history, occupational history and history of recent travel.
- Careful and repeated physical examination is of crucial importance. This should include a detailed examination of the skin, optic fundus and lymph nodes. The heart should be examined for murmurs and abdomen for splenic enlargement.
- The pattern of fever should be documented with simultaneous pulse record.

Laboratory Tests

- Complete blood counts, ESR and peripheral smear examination for parasites and abnormal cells.
- Microscopic examination and culture of urine.
- Culture and examination of the stool for ova, parasites and occult blood.
- Aerobic and anaerobic cultures of the blood.
- Blood chemistries including renal and liver function tests.
- Mantoux test and fungal skin tests.
- Gastric aspirate examination by smear and culture for tubercle bacilli.
- Serological tests including ASO titre, rheumatoid factor, antinuclear antibodies, viral antibody titres, Paul Bunnell test and brucella agglutination test.
- Radiographic examination including chest radiography, barium GI series, echocardiography, ultrasonography of abdomen and pelvis, CT scan of abdomen and thorax and isotope scans.
- Bone marrow biopsy, liver biopsy and lymph node biopsy.
- Radionuclide scintigraphy including ^{67}gallium citrate scintigraphy, ^{111}In-labelled leucocyte scintigraphy and ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) to detect inflammatory conditions. PET is also useful in diagnosing neoplastic conditions.
- Diagnostic surgical procedures like peritoneoscopy, laparoscopy, bronchoscopy and exploratory laparotomy may rarely be required.

Treatment

- Treatment of underlying causes detected after investigations.
- Empirical broad-spectrum antibiotics.
- Empirical antitubercular treatment.
- Rheumatic fever and Still's disease respond dramatically to aspirin and NSAIDs.
- Temporal arteritis and polymyalgia rheumatic respond to glucocorticoids dramatically.

Q. What are the serological methods in infectious diseases?

Q. Describe various immunoassays.

- Serological method typically detects proteins, be it an antibody or an antigen in serum.
- The term "immunoassay" is a broad term used for a biochemical test that measures the concentration of a substance in a biological liquid, typically serum or urine, using the reaction of an antibody or antibodies to its antigen.

ELISA

- The enzyme-linked immunosorbent assay (ELISA) is a serological technique used mainly to detect the presence of an antibody or an antigen in a sample.
- Enzyme immunoassay (EIA) is a synonym for the ELISA.
- Performing an ELISA involves at least one antibody with specificity for a particular antigen.
- The sample with an unknown amount of antigen (or antibody) is immobilised on a solid support (usually a polystyrene microtitre plate) either nonspecifically (via adsorption to the surface) or specifically (via capture by another antibody specific to the same antigen in a "sandwich" ELISA).
- After the antigen is immobilised, the detection antibody is added, forming a complex with the antigen. The detection antibody can be covalently linked to an enzyme or can itself be detected by a secondary antibody that is linked to an enzyme through bioconjugation.

- Between each step, the plate is typically washed with a mild detergent solution to remove any proteins or antibodies that are not specifically bound.
- After the final wash step, the plate is developed by adding an enzymatic substrate to produce a visible signal that indicates the quantity of antigen in the sample.

Immunohistochemistry

- Immunohistochemistry or IHC refers to the process of localizing proteins in cells of a tissue section exploiting the principle of antibodies binding specifically to antigens in biological tissues. It takes its name from the roots "immuno", in reference to antibodies used in the procedure and "histo", meaning tissue.
- Immunohistochemical staining is widely used in the diagnosis and treatment of cancer, but it is also of use in infectious diseases as several antigens of microorganisms can be detected in tissues.

Immunodiffusion

- Immunodiffusion is a diagnostic test that involves diffusion of antibody containing sample through a substance such as agar.

Immunoelectrophoresis

- Electrophoresis of a determined antigen mixture in an agarose gel allows separation of different proteins along the gel slide and then the lateral diffusion in the gel of an immune serum or a monoclonal antibody is noted.
- If some antibodies are specific to one of the antigens, the precipitation of the antigen–antibody complexes produces a precipitation arc.
- This method is very useful to determine the number of antigens recognised against a particular mixture of antigen (e.g. crude parasite extracts).

Q. What are the various molecular methods used in diagnosis of infectious diseases?

- Most often these methods are used to identify a nucleic acid, either DNA or RNA.
- In the last two decades, techniques of molecular biology have been extensively used in various fields of infectious diseases. These include:
  - Epidemiology of infectious diseases (to determine whether a single strain of a microbe is responsible for most of the cases in an epidemic).
  - Diagnosis of infectious diseases.
  - Identification of new species or organisms.
  - Prevention of infectious diseases.
- Molecular tests provide several advantages over serological tests. They detect the microbe instead of a serological history of the infection and are usually able to detect the presence of a microbe much earlier in the course of an infection. However, false positive results may occur due to sample contamination.
- Various techniques used in molecular biology are described below.

Restriction Enzymes and Gel Electrophoresis

- The DNA can be cut into a number of fragments by the enzymes called restriction enzymes. These enzymes are obtained from bacteria.
- Restriction enzymes recognise specific DNA sequences and cut the double-stranded DNA at these sites only.
- Depending on the enzyme used, DNA is thus cut into small fragments with great reproducibility.
- This fragmented DNA can be separated according to the size and charge into fragments using electrophoresis on a gel matrix.
- DNA is added at one end of the gel and current is applied across it. The small fragments of DNA move towards the anode.
- Fragment sizes can be determined by running the fragments of known size on the same gel.

Southern Blotting and DNA Probes

- DNA probe is a piece of single-stranded DNA that can be labelled with a radioactive isotope (^{32}P) or a fluorescent signal (biotin and digoxigenin-11-UTP).
- After electrophoresis on a gel, the separated DNA fragments are transferred to a blotting paper.
- A DNA probe is used to indicate whether a particular fragment is present in the DNA or not. DNA probe will bind to a complementary (homologous) DNA.
- Radioactivity is detected by radioactive technique while fluorescence is detected by a UV lamp.
- As the structure of probe is known, the structure of complementary strand of DNA is easily identified.
- This is the basis of Southern blotting (after EM Southern who described the procedure first).

DNA Microarray

- It is reverse of DNA probes in which known DNA (large oligonucleotides or complementary DNA) is immobilised on a glass slide and the unknown DNA is labelled to make a probe.
- A microarray is so-called because it can comprise 20,000 or more different known DNAs, each DNA being spotted onto glass slides to form the array.

Northern Blotting

- It is similar to the procedure of Southern blotting except that here RNA fragments are used instead of DNA fragments (northern is not the name of a person).

Western Blotting

- It is used to blot proteins (again, western is not the name of a scientist).

DNA cloning

- A particular DNA of interest whose structure is known, can be inserted into an inactive virus that is used as a vector.
- The DNA fragment can also be linked to a plasmid.
- Cutting and joining are done by restriction endonucleases and ligases, respectively.
- When the vector is introduced into another organism, e.g. *E. coli*, and cultured in a suitable medium, replication of bacteria results in multiple copies or clones of the inserted DNA sequence.
- Bacteria that have successfully taken up the recombinant plasmid can be selected, if the plasmid also carries an antibiotic resistance gene and the culture is done in presence of that particular antibiotic.
- Insulin has been prepared in large amounts using this method.

Polymerase Chain Reaction (PCR)

- It is a method to amplify a minute amount of DNA within a few hours.
- The double-stranded DNA is denatured by heat into single-stranded DNA.
- DNA primers of interest are added along with the four basic deoxynucleotides and the solution is cooled. This results in binding of DNA probes to their target DNA.
- DNA polymerase is used to extend the primers in opposite directions using target DNA as a template.
- This cycle is repeated several times that results in production of millions of copies of the original DNA.
- Used in medical and biological research laboratories for a variety of tasks, such as sequencing of genes, diagnosis of hereditary diseases, identification of genetic fingerprints (used in forensics and paternity testing), detection and diagnosis of infectious diseases and creation of transgenic organisms.
- In reverse transcriptase PCR (RT-PCR), RNA from the sample is converted to DNA using a retrovirus reverse transcriptase polymerase and the DNA is amplified by PCR.
- In real time PCR, the rate of DNA amplification is monitored as an indication of the initial concentration of sample DNA.

Q. Discuss early goal-directed therapy for severe sepsis and septic shock.

- Speed and appropriateness of therapy administered in the initial hours after severe sepsis or septic shock develops are likely to influence outcome. Surviving Sepsis Campaign is an international effort to increase awareness and improve outcomes in severe sepsis.
- An early goal-directed therapy has been advocated to reduce morbidity and mortality in patients with severe sepsis and shock.
- Acute respiratory distress syndrome (ARDS) often develops in these patients and requires appropriate management.

Initial Resuscitation and Infection Control (First 3–6 Hours)

Resuscitation

- Resuscitation should be started as soon as hypoperfusion is recognised (hypotension or serum lactate >4 mmol/L) and should not be delayed pending ICU admission.
- During the first 6 hours of resuscitation, the goals of initial resuscitation, include all of the following:
  - CVP 8–12 mmHg (≥12 mmHg in mechanically ventilated patients)
  - Mean arterial pressure ≥65 mmHg
  - Urine output ≥0.5 mL/kg/hour
  - Central venous oxygen saturation ≥70% or mixed venous oxygen ≥65%
- If venous oxygen saturation target is not achieved:
  - Consider further fluid
  - Transfuse packed red blood cells to haematocrit of ≥30% and/or
  - Start dobutamine infusion, maximum 20 µg/kg/min.

Fluid Therapy

- Administer crystalloids or colloids for resuscitation.
- Give fluid challenges of 30 ml/Kg of crystalloids for hypotension or lactate > 4 mmol/L over 30 minutes.
- Rate of fluid administration should be reduced if cardiac filling pressures increase without concurrent haemodynamic improvement.

Diagnosis

- Obtain appropriate cultures before starting antibiotics.
- Obtain two or more blood cultures (one or more blood cultures should be percutaneous; one blood culture from each vascular access device in place ≥48 hours).
- Culture other sites as clinically indicated.
- Perform imaging studies promptly to confirm and to identify any source of infection.

Antibiotic Therapy

- Begin intravenous antibiotics as early as possible and always within the first hour of recognising severe sepsis and septic shock.
- Broad-spectrum antibiotics active against likely agents to be started.
- Reassess antimicrobial regimen daily to optimise efficacy to prevent resistance and to avoid toxicity.
- Consider combination therapy if *Pseudomonas* infection is suspected.
- Consider empiric therapy in neutropenic patients.
- Administer combination therapy for 3–5 days and de-escalate following culture/susceptibilities reports.
- Duration of therapy typically limited to 7–10 days longer if response is slow or there are undrainable foci of infection or immunologic deficiencies.
- Stop antimicrobial therapy if cause is found to be non-infectious.

Source Identification and Control

- A specific anatomic site of infection should be established as rapidly as possible within first 6 hours of presentation.
- Evaluate patient for a focus of infection amenable to source control measures (e.g. abscess drainage and tissue debridement).
- Implement source control measures as soon as possible following successful initial resuscitation.
- Remove intravascular access devices if potentially infected.

Vasopressors

- Maintain Mean arterial pressure (MAP) ≥65 mmHg.
- Norepinephrine is generally administered as the initial vasopressors of choice.
- Dopamine as an alternative vasopressor agent to norepinephrine, may be used only in highly selected patients (e.g., patients with low risk of tachyarrhythmias and absolute or relative bradycardia)
- Epinephrine, phenylephrine or vasopressin should not be administered as the initial vasopressor in septic shock. Vasopressin 0.03 units/minute may be subsequently added to norepinephrine.
- Use epinephrine as the first alternative agent in septic shock when blood pressure is poorly responsive to norepinephrine or dopamine.
- Do not use low-dose dopamine for renal protection.
- In patients requiring vasopressors, insert an arterial catheter as soon as practical.

Inotropic Therapy

- Use dobutamine in patients with myocardial dysfunction as supported by elevated cardiac filling pressures and low cardiac output.
- Do not increase cardiac index to predetermined supranormal levels.

Steroids

- Consider intravenous hydrocortisone for adult septic shock when hypotension responds poorly to adequate fluid resuscitation and vasopressors.
- ACTH stimulation test is not recommended to identify the subset of adults with septic shock who should receive hydrocortisone.
- Hydrocortisone is preferred to dexamethasone.
- Steroid therapy may be weaned once vasopressors are no longer required.
- Hydrocortisone dose should be ≤300 mg/day as continuous infusion and not as repeated doses.
- Do not use corticosteroids to treat sepsis in the absence of shock unless the patient's endocrine or corticosteroid history warrants it.

Recombinant Human Activated Protein C

- At present, rhAPC is NOT recommened in patients with sepsis-induced organ dysfunction.

Other Supportive Treatments

Blood Product Administration

- Give red blood cells when haemoglobin decreases to <7.0 g/dL to target a haemoglobin of 7.0–9.0 g/dL in adults. A higher haemoglobin level may be required in special circumstances (e.g. myocardial ischaemia, severe hypoxaemia, acute haemorrhage, cyanotic heart disease or lactic acidosis).
- Do not use erythropoietin to treat sepsis-related anaemia.
- Do not use fresh frozen plasma to correct laboratory clotting abnormalities unless there is bleeding or planned invasive procedures.
- Do not use antithrombin therapy.
- Administer platelets when:
  - Platelet counts are 10,000/mm^3, regardless of bleeding.
  - Platelet counts are 10,000–20,000/mm^3 and there is significant bleeding.
  - Higher platelet counts ($\geq$50,000/mm^3) are required for surgery or invasive procedures.

Mechanical Ventilation of Sepsis-Induced ARDS

- Target a tidal volume of 6 mL/kg in patients with ARDS.
- Target an initial upper limit plateau pressure $\leq$30 cm H$_2$O.
- Allow PaCO$_2$ to increase above normal, if needed, to minimise plateau pressures and tidal volumes.
- Set positive end-expiratory pressure to avoid extensive lung collapse at end expiration.
- Consider using the prone position for ARDS patients requiring potentially injurious levels of FiO2 or plateau pressure, provided they are not put at risk from positional changes.
- Maintain mechanically ventilated patients in a semirecumbent position (head of the bed raised to 45°) unless contraindicated
- Do not use a pulmonary artery catheter for the routine monitoring of patients with ARDS.
- Use a conservative fluid strategy for patients with established ARDS who do not have evidence of tissue hypoperfusion.

Sedation, Analgesia and Neuromuscular Blockade in Sepsis

- Use either intermittent bolus sedation or continuous infusion sedation with daily interruption/lightening to produce awakening.
- Avoid neuromuscular blockers where possible.

Glucose Control

- Use intravenous insulin to control hyperglycaemia in patients with severe sepsis following stabilisation in the ICU.
- Aim to keep blood glucose $\leq$180 mg/dL.
- Provide a glucose calorie source and monitor blood glucose values for every 1–2 hours (4 hours when stable) in patients receiving intravenous insulin.

Renal Replacement

- Intermittent haemodialysis and continuous veno-venous haemofiltration (CVVH) are considered equivalent.
- CVVH offers easier management in haemodynamically unstable patients.

Bicarbonate Therapy

- Do not use bicarbonate therapy for the purpose of improving haemodynamics or reducing vasopressor requirements when treating hypoperfusion-induced lactic acidosis with pH $\geq$7.15.

Deep Vein Thrombosis Prophylaxis

- Use either unfractionated heparin or low molecular weight heparin, unless contraindicated.
- Use a mechanical prophylactic device such as compression stockings or an intermittent compression device when heparin is contraindicated.
- Use a combination of pharmacologic and mechanical therapy for patients who are at very high risk for deep vein thrombosis.

Stress Ulcer Prophylaxis

- Provide stress ulcer prophylaxis using H$_2$ blocker or proton pump inhibitor in patients with high risk of GI bleed (e.g., coagulopathy, mechanical ventilation for at least 48 h). Benefits of prevention of upper gastrointestinal bleed must be weighed against the potential for development of ventilator-acquired pneumonia.

Oral Decontamination

- Oral chlorhexidine gluconate be used as a form of oropharyngeal decontamination to reduce the risk of ventilator-associated pneumonia in ICU patients.

Experimental Therapies

- Experimental therapies include the use of anti-inflammatory medications, antiendotoxin therapy and anticytokine therapy.

Surviving Sepsis Campaign Care Bundles

To be completed within 3 hours:	To be completed within 6 hours:
• Measure lactate level	• Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mmHg
• Obtain blood cultures prior to administration of antibiotics	
• Administer broad spectrum antibiotics	
• Administer 30 mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L	• In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥ 4 mmol/L (36 mg/dL):
	• Measure central venous pressure (CVP)*
	• Measure central venous oxygen saturation (ScvO2)*
	• Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥ 8 mm Hg, $ScvO_2$ of ≥ 70% and normalization of lactate.

Q. Discuss the aetiology, clinical features, complications and prevention of measles (rubella).

- Measles is caused by a paramyxovirus (RNA virus) infection.
- Mode of spread is by droplet infection.
- Incubation period is of about 10 days.
- Period of infectivity is from 4 days before and 2 days after the onset of rash. People with compromised immunity can continue to shed virus for the entire duration of illness.

Clinical Features

Catarrhal Stage

- The patient is highly infective during this stage.
- Febrile onset with nasal catarrh, sneezing, conjunctival redness, watering of eyes, photophobia, conjunctivitis, malaise, irritability and cough.

Koplik's Spots

- Koplik's spots are small, red and irregular lesions on the buccal mucosa with blue-white centres (enanthem). They appear 1–2 days before the onset of the maculopapular rash and disappear 1–2 days after the appearance of the rash. They are best seen at the opening of the parotid duct (upper 2nd molar tooth). The lesions consist of vesicle formation and epithelial necrosis.

Exanthematous Stage

- Red and maculopapular rashes are first seen over the back of the ears and forehead, later spreading downwards over the face, neck, trunk and feet. The rash may also have some petechiae
- The malaise and fever subside as the rash fades that takes 4–5 days.

Complications

• Bronchiolitis, bronchitis	• Myocarditis
• Interstitial giant cell pneumonia	• Hepatitis
• Bronchopneumonia, bacterial pneumonia	• Enteritis
• Conjunctivitis, keratitis, corneal ulcers	• Acute glomerulonephritis
• Subacute sclerosing panencephalitis (SSPE)	• Thrombocytopenia

- CNS complications may occur early (acute post-infectious measles encephalitis) or after years of viral persistence (sub-acute sclerosing panencephalitis).
- Signs and symptoms of SSPE appear an average of 7 years after the initial infection and include personality changes, myoclonic seizures and motor disturbances followed by coma and death.

Treatment

- It is supportive and includes antipyretics, fluids, and treatment of bacterial superinfections.
- Administration of vitamin A to children with measles may reduce morbidity and mortality.
- In SSPE, use of ribavirin and intraventricular interferon-α may prolong the disease course.

Prevention

- Passive immunisation: Human normal immunoglobulin may be given intramuscularly. Indications for passive immunisation are given below.
  - Contacts under 12 months of age
  - Debilitated children, especially those with a malignant disease.
  - Pregnant females
  - Patients with active tuberculosis
  - Immunodeficient patients and those with malignant diseases
- Active immunisation: Live attenuated measles virus is given as a subcutaneous injection. This vaccination can offer protection for at least 15 years. It can be given simultaneously in combination with rubella and mumps vaccines (MMR vaccine). Vaccination within 72 hours of exposure is the intervention of choice for susceptible individuals older than 12 months of age. Measles vaccination is contraindicated in:
  - Pregnant females
  - Patients with untreated tuberculosis
  - Patients with leukaemias and lymphomas
  - Immunocompromised patients (children with asymptomatic HIV-infection can receive the vaccine).

Q. Give a brief account of rubella (German measles, "3-day measles"), expanded rubella syndrome and congenital rubella or rubella syndrome.

- Rubella is caused by a togavirus infection.
- Mode of spread is by droplet infection.
- Incubation period is about 18 days.
- The prodromal or catarrhal stage is characterised by malaise, headache, fever, mild conjunctivitis and lymphadenopathy (suboccipital).
- The exanthematous stage is characterised by pink macular rashes first appearing behind the ears and on the forehead, later spreading downwards to the trunk and extremities. The rashes typically last 3 days. Although the distribution of the rubella rash is similar to that of measles, the spread is much more rapid and the rash does not darken or coalesce. An enanthem on the soft palate (Forchheimer spots) may be seen.
- There may be associated polyarthritis and generalised lymphadenopathy that may persist for 2 weeks.
- Important complications include post-infectious encephalitis, thrombocytopenia, spontaneous abortion and congenital rubella syndrome.

Congenital Rubella or Rubella Syndrome

- Congenital rubella results from the transplacental transmission of the virus to the foetus from an infected mother. The highest risk is during the first trimester of pregnancy.

Congenital malformations associated with rubella syndrome	
- Congenital heart diseases	Patent ductus arteriosus, ventricular septal defect, pulmonic stenosis
- Ophthalmic diseases	Corneal clouding, cataracts, chorioretinitis, microphthalmia, blindness
- Deafness	
- Mental retardation	
- Microcephaly	

Expanded Rubella Syndrome

- Expanded rubella syndrome additionally includes the following manifestations:
  - Hepatosplenomegaly

- Thrombocytopenic purpura
- Intrauterine growth retardation
- Myocarditis
- Interstitial pneumonia
- Humoral and cellular immunodeficiency.

Prevention

- Active immunisation can be given with rubella vaccine. This is a live attenuated vaccine.
- The aim of vaccination is to decrease the frequency of infection in the population and thus, decrease the chance of susceptible pregnant females being exposed to the infection.
- It should be given to all children at the age of 15 months along with mumps and measles vaccine (MMR vaccine). A second dose is given to young females aged 11–13 years. Seronegative females of childbearing age should also be offered the vaccine.
- Rubella vaccine must never be given to pregnant females or to those who may become pregnant within 3 months of immunisation, because of the high risk of vaccine virus induced foetal damage. It is also contraindicated in patients with immune deficiency diseases and those who are taking immunosuppressive drugs.

Q. Discuss the clinical manifestations, complications and prevention of mumps.

- Mumps is caused by a paramyxovirus.
- Mode of spread is by droplet infection.
- Incubation period is about 15–20 days.

Clinical Features

- Prodromal symptoms consist of malaise, anorexia, feverishness and tenderness at the angle of the jaw. This is followed by typical parotitis. Parotitis is bilateral in two-thirds of the cases and remains confined to one side in the remainder. The chief complaints are difficulty in eating, swallowing and talking.

Complications

- Epididymo-orchitis, oophoritis
- Pancreatitis
- Encephalomyelitis, mumps meningitis
- Mumps myocarditis
- Thrombocytopenic purpura.

Prevention

- Mumps vaccine is given at the age of 15 months along with measles and rubella vaccines (MMR vaccine).

Q. What are the common herpes viruses infecting humans? Enumerate the diseases caused by them.

- There are eight herpes viruses infecting humans. These have double-stranded DNA. The viruses and the diseases caused by them are briefed in the information box.

Virus	Diseases
Herpes simplex virus	
• Type 1	Herpes labialis, keratoconjunctivitis, dendritic corneal ulcer, pulp space infections (whitlows), encephalitis with temporal lobe involvement, genital herpes (40%), pneumonitis, tracheobronchitis, ulcerative stomatitis, oesophagitis
• Type 2	Genital herpes (60%), neonatal infections
Cytomegalovirus	Congenital infections (intrauterine growth retardation), perinatal infections, infections in the immunocompromised patients (pneumonitis, retinitis)
Epstein–Barr virus (EBV)	Infectious mononucleosis, Burkitt's lymphoma, nasopharyngeal carcinoma, hairy leucoplakia in AIDS patients
Varicella–zoster virus	Chickenpox herpes-zoster (shingles)
Human herpes virus 6	Exanthem subitum (sixth disease)
Human herpes virus 7	Exanthem subitum (sixth disease)
Human herpes virus 8	Kaposi's sarcoma, multicentric Castleman's disease

Q. Discuss the aetiology, clinical features, investigations, complications and treatment of infectious mononucleosis (glandular fever).

Aetiology

- Caused by EBV, a herpes virus that infects and replicates in B lymphocytes and oropharyngeal epithelial cells. Transmission is largely by salivary contact, e.g. kissing.
- Peak incidence in 14–16 years for young females and 16–18 years for young males.
- Incubation period is 7–10 days.
- Subclinical infection is very common.

Clinical Features

- Constitutional symptoms, especially fever.
- Severe pharyngitis and tonsillitis.
- Lymphadenopathy (particularly posterior cervical lymph node enlargement but sometimes generalised) and hepato-splenomegaly.
- Petechial rashes on palate.
- Maculopapular rash.
- Ampicillin or amoxycillin induces maculopapular eruptions in more than 90% of patients.

Investigations

- Peripheral blood lymphocytosis with atypical lymphocytes (>20%).
- Elevated liver enzymes.
- Circulating heterophil antibodies are directed against viral antigens that cross-react with antigens found on sheep and horse red cells. Heterophile antibody tests are negative in 25% of patients during the first week of infection and in 5–10% during or after the second week. Can be detected by:
  - Positive monospot test (rapid screening test)—horse red cells agglutinate on exposure to heterophile antibodies.
  - Positive Paul Bunnell test—sheep red blood cells agglutinate in the presence of heterophile antibodies.
- Viral serologic tests specific for EBV may be positive.
  - IgM antiviral capsid antibodies
  - Antibodies to EBV early antigen
  - EBV nuclear antigen proteins.

Complications

- Chronic fatigue syndrome
- Haemolytic anaemia and thrombocytopenia
- Aplastic anaemia, thrombotic thrombocytopenic purpura or haemolytic–uraemic syndrome and disseminated intravascular coagulation (DIC)
- Glomerulonephritis, interstitial nephritis
- Hepatitis
- Myocarditis, pericarditis
- Splenic rupture
- Neurologic complications, e.g. meningoencephalitis, transverse myelitis and Guillain-Barre (GB) syndrome
- Airway obstruction due to severe pharyngeal oedema.

Treatment

- Infectious mononucleosis is usually a self-limiting disease requiring no specific treatment.
- Symptomatic treatment includes rest, acetaminophen, etc.
- Corticosteroids are indicated in certain specific complications (meningitis, encephalitis, severe haemolysis and severe pharyngeal oedema).

Q. Discuss the clinical manifestations, complications and management of chickenpox.

- Chickenpox is caused by primary infection with varicella-zoster virus, also known as human herpes virus 3. Following primary infection virus remains latent; afterwards, re-activation gives rise to herpes zoster.
- Mode of transmission is by droplet infection from the upper respiratory tract or from the discharge by ruptured lesions on the skin.
- The incubation period is about 14–21 days.
- The disease is contagious till pustules disappear.

Clinical Features

- The characteristic rash first appears on the trunk on the 2nd day of illness and then the face, and finally on the limbs. The lesions are maximum on the trunk and minimum on the periphery of the limbs.
- The characteristic lesions appear as macules and progress to papules, vesicles and pustules. The lesions finally dry up to form scabs.
- The lesions appear in crops so that lesions at all stages of development are seen in any area at the same time.
- Low-grade fever is often present.
- In immunocompromised patients the lesions are haemorrhagic and are numerous. Dissemination to other organs is quite frequent.

Complications

• Myocarditis	• Meningitis
• Hepatitis	• Acute glomerulonephritis
• Corneal lesions	• Interstitial pneumonia
• Bleeding diathesis	• Arthritis, osteomyelitis
• Perinatal varicella	• Congenital varicella
• Cerebellar ataxia	• Reye's syndrome with aspirin use

Diagnosis

- Mainly clinical.
- A Tzanck smear of vesicular fluid demonstrates multinucleated giant cells and epithelial cells with eosinophilic intra-nuclear inclusion bodies.
- Isolation of virus through culture of vesicular fluid.
- Direct immunofluorescence test to detect virus is easier than culture.
- PCR is to identify viral gene.

Management

- No treatment is required in majority of cases.
- Symptomatic treatment includes antihistamines and local calamine lotion.
- Acyclovir (15 mg/kg five times a day for 7 days) can be used in adults or immunocompromised patients. It reduces complications of chickenpox, particularly if given within 24 hours. In immunocompromised patients, acyclovir is generally given intravenously. Other drugs that can be used include valaciclovir (1000 mg TID) and famciclovir (500 mg TID).
- In healthy children, use of antiviral agents may reduce the duration of disease when given within 24 hours of symptoms. However, since the disease is generally self-limiting and symptoms can be controlled and reduced with supportive therapy, antivirals are often not given in children unless they are immunocompromised or on long-term salicylate therapy when Reye's syndrome may develop.
- Secondary bacterial infection is treated with local antiseptic or systemic antibiotics like cloxacillin.

Prophylaxis

- A live attenuated vaccine is available for the prevention of chickenpox in immunocompetent children and adults who are at a high risk of infection. It should not be given to pregnant or immunocompromised patients.
- Passive prophylaxis using zoster immune globulin (ZIG) or varicella zoster immune globulin (VZIG) may be given to immunocompromised persons or pregnant women with history of significant exposure within last 96 hours. It should also be given prophylactically to an infant whose mother develops chickenpox up to 7 days before delivery or if the mother develops chickenpox up to 28 days after delivery.

Q. Discuss briefly about human papillomaviruses.

- Human papillomaviruses (HPVs) are double-stranded DNA tumour viruses with strong tropism to stratified squamous epithelial cells of skin and mucous membranes.
- Do not cause viraemia or death of infected epithelial cells.
- Most commonly cause benign papillomas and warts.
- Some types of HPV are oncogenic that can cause anogenital tumours.
- Genital HPV is divided into high-risk and low-risk types—high-risk genital types are associated with intraepithelial neoplasias that can develop into invasive carcinomas; low-risk genital types are responsible for condylomata acuminata and low-grade cervical dysplasias with a low risk of development of invasive carcinoma.

- Infection usually occurs via direct skin or mucous membrane contact. Autoinoculation is another means of spread of HPV infection. Anogenital HPV infections are usually transmitted sexually and are often detected at several sites simultaneously (multifocal infection).
- Most important risk factor in transmission of genital HPV is number of sexual partners.
- Incubation period for genital HPV infection varies from weeks to months.
- Majority of infections are subclinical. Further, 80% of infection resolves spontaneously within 12 months.

Diseases Produced by HPV

• Verrucae plantaris	Usually involve hands and feet (verrucae palmares, verrucae plantaris) Skin coloured Flat or dome-shaped papules Surface rough and hyperkeratotic Usually asymptomatic; however at pressure sites, endophytic growth can be very painful
• Verrucae planae	Flat, reddish or skin coloured papules Mainly involve face, hands or distal forearms
• Periungual warts	Present at nail fold; often painful
• Skin cancers (squamous cell carcinoma and basal cell carcinoma)	May act synergistically with ultraviolet light Usually not caused by high-risk HPV
• Condylomata acuminate	Caused by low-risk HPV Can occur on the external or internal genitalia, perianally, in the anal canal, perineum Multiple, flat or raised exophytic papillomas May be pedicled or broad based Usually self-limited

• Anogenital malignancies
  • Intraepithelial neoplasms
  • Penile carcinoma
  • Cervical carcinoma
	Caused by high-risk HPV Can involve cervix, vulva, vagina, anus and penis — HPV cause about 70% of all cervical carcinomas Squamous cell carcinoma more common than adenocarcinoma of cervix

• Others
  • Oral lesions
  • Head and neck cancers
	May be asymptomatic or cause papilloma Usually involve oropharynx, tonsils, base of tongue and soft palate

Diagnosis

- Based on clinical presentation.
- May require biopsy to confirm dysplasia or carcinoma.
- Acetic acid: Subclinical HPV infections can be visualised after application of 3–5% acetic acid with a cotton swab; whitening of HPV-positive lesions occur in 5 minutes.
- Endoscopic evaluation (colposcopy and proctoscopy) to visualise condyloma, dysplasia and carcinomas.
- Molecular methods to detect viral DNA (e.g. hybrid capture 2 DNA test).
- PCR to detect viral DNA.

Therapy

- No specific antiviral agent is available.
- Verrucae
  - Keratolysis: After mechanical removal of the mass with a sharp knife, verrucae resolve under application of salicylic acid: lactic acid: collodion (1:1:4). Vaseline is applied to the surrounding skin to protect it from chemical corrosion.
  - Cryotherapy: Cryotherapy using liquid nitrogen is used to freeze warts.
- Anogenital warts
  - Podophyllotoxin: It produces death of infected cells. It is applied twice a day for 3 consecutive days in cycles consisting of several weeks. One advantage of this treatment is that patients can perform it at home. Serious systemic

side effects can occur if it is applied to larger surface areas and absorbed systemically. Use during pregnancy is contraindicated.

- Imiquimod: Imiquimod induces the production of antiviral cytokines such as interferon and tumour necrosis factor alpha. A 5% cream is applied thrice weekly for up to 4 months.
- Ablation by surgery, laser and electrocauterisation.
- Cryotherapy using liquid nitrogen.
- Trichloroacetic acid: Topical application of 50–90% of trichloroacetic acid leads to coagulation of cell protein with subsequent cell death.
- 5-Fluorouracil applied as cream.

HPV Vaccines

- After parenteral administration, high titres of antibodies are induced that can neutralise infectious viruses.
- Two commercially available HPV vaccines: Quadrivalent vaccine and bivalent vaccine.
- Can prevent about 70% of cervical dysplasias.

Q. How do you classify arboviruses? Enumerate the major clinical syndromes caused by arboviruses.

- Arboviruses are viruses that are maintained in nature through biological transmission between susceptible vertebrate hosts by haematophagous arthropods (arthropod-borne diseases). They multiply and produce viraemia in the vertebrates, multiply in the tissues of arthropods and are passed on to new vertebrates by the bites of arthropods after a period of extrinsic incubation.
- Arboviruses belong to several families. Important families and the diseases caused are listed below.

Family	Common diseases
• Arenaviridae	Lymphocytic choriomeningitis Lassa fever
• Bunyaviridae	California encephalitis Sandfly fever Congo haemorrhagic fever Hantaan fever (HERS)
• Filoviridae	Marbola disease Ebola disease
• Flaviviridae	Yellow fever Dengue fever Japanese encephalitis Kyasanur forest disease (KFD) West Nile encephalitis St. Louis encephalitis
• Togaviridae	Sindbis disease Chikungunya disease Eastern equine encephalitis Western equine encephalitis

Major Clinical Syndromes

- Based on the major symptoms produced by an arbovirus, the major clinical syndromes are as listed below.

Fever, Arthralgia, Myalgia, Rash Syndrome

- Chikungunya
- Sandfly fever
- Dengue fever
- Lymphocytic choriomeningitis.

Encephalitis/Aseptic Meningitis

- Eastern equine encephalitis
- Western equine encephalitis
- Japanese encephalitis.

Haemorrhagic Fever

- Yellow fever
- Kyasanur forest disease (KFD)
- Dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS)
- Haemorrhagic fever with renal syndrome (HFRS).

Q. Describe classic dengue (breakbone fever), dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS).

Q. Discuss dengue with and without warning features and describe also severe dengue.

- An estimated 50 million dengue infections occur annually.
- Caused by four distinct subgroups of dengue viruses, types 1, 2, 3 and 4 (DEN 1–4) which are RNA viruses.
- The genome of DEN virus encodes different gene products: C (capsid), prM (matrix), E (envelope) and seven non-structural (NS) proteins. NS1 protein is secreted in plasma and is useful in early diagnosis.
- Dengue infection of humans occurs from bites of *Aedes aegypti* mosquitoes.
- The mosquito feeds during the day and has a propensity for man-made habitats containing water.
- Dengue viral infection can present as three broad clinical patterns:
    - Classic dengue
    - Haemorrhagic fever
    - Undifferentiated fever

Manifestations of Dengue Virus Infections
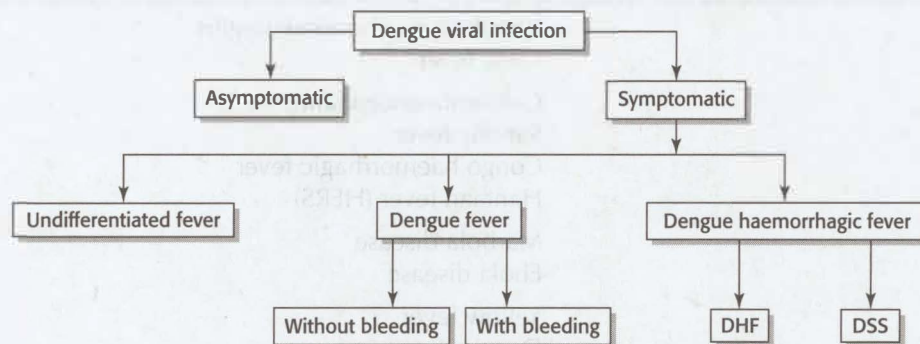
- Presently, WHO classifies dengue viral infections into non-severe dengue (with and without warning signs) and severe dengue. However, it should be kept in mind that even dengue patients without warning signs may develop severe dengue.

New Classification of Dengue

Non-severe dengue without warning signs	Non-severe dengue with warning signs	Severe dengue
Probable dengue	*Presence of warning signs*	• Severe plasma leakage leading to
• Live in/travel to endemic area	• Abdominal pain or tenderness	• Shock (DSS)
• Fever and two of the following criteria:	• Persistent vomiting	• Fluid accumulation with respiratory distress
• Nausea and vomiting	• Clinical fluid accumulation	• Severe bleeding
• Rash	• Mucosal bleed	• As evaluated by clinician
• Aches and pains	• Lethargy and restlessness	• Severe organ involvement
• Tourniquet test positive	• Liver enlargement >2 cm	• Liver: AST or ALT ≥1000
• Leucopenia	• Laboratory: Increase in haematocrit concurrent with rapid decrease in platelet count	• CNS: Impaired consciousness
• No warning sign		• Heart and other organs
Laboratory-confirmed dengue		
• See under "Diagnosis"		

Pathogenesis of Severe Dengue

- Occurs in persons who were infected with one serotype of dengue virus previously and therefore have antibodies against that particular serotype.
- A second infection by a different serotype causes immunologic enhancement of antibody acquired from a previous infection.
- Antibody–virus complex taken up by macrophages.
- Production of vascular permeability factors by macrophages.
- These vascular permeability factors induce plasma leakage, resulting in DHF and ultimately, DSS.

Clinical Features

- After the incubation period of 5–8 days, the illness begins abruptly and is followed by the three phases—febrile, critical and recovery.

Febrile Phase

- Patients typically develop high-grade fever suddenly that usually lasts for 2–7 days.
- Often accompanied by facial flushing, skin erythema, generalised body ache, myalgia, arthralgia, severe back ache ("breakbone" fever), retro-orbital pain and headache.
- Sore throat, injected pharynx and conjunctival injection in some patients.
- Anorexia, nausea and vomiting.
- High fever may cause febrile seizures in children.
- In some cases, temperature may decrease to nearly normal after 3–4 days and other symptoms disappear; this remission lasts for 2 days and is followed by return of fever and other symptoms. This is known as "saddleback fever" fever.
- Tenderness upon pressure on eyeball.
- A positive tourniquet test may be present.
- Mild haemorrhagic manifestations like petechiae and mucosal membrane bleeding may be seen.
- Liver is often enlarged and tender.
- These features occur in both severe and non-severe dengue cases. Therefore monitoring for warning signs and other clinical parameters is crucial for recognising progression to critical phase.
- Earliest laboratory abnormality is a progressive decrease in total white cell count, which should alert the physician to a high probability of dengue.

Tourniquet Test

- Apply blood pressure cuff and mark a circle with an area of about 2.5 cm² (roughly the size of diaphragm of stethoscope)
- Inflate the cuff to a point mid-way between the systolic and diastolic pressures for 5 minutes
- A test is considered positive when 20 or more petechiae appear in the circle

Critical Phase

- Around the time of defervescence of fever, an increase in capillary permeability along with increasing haematocrit levels may occur. This marks beginning of critical phase. The degree of increase above the baseline haematocrit often reflects severity of plasma leakage.
- The period of clinically significant plasma leakage usually lasts for 24–48 hours.
- Progressive leucopenia followed by a rapid decrease in platelet count usually precedes plasma leakage.
- Patients without an increase in capillary permeability will improve, while those with increased capillary permeability may become worse as a result of lost plasma volume.
- Pleural effusion and ascites may be detectable.
- Shock occurs when a critical volume of plasma is lost through leakage. It is often preceded by warning signs.
- Body temperature may be subnormal when shock occurs.
- With prolonged shock, organ hypoperfusion results in progressive organ impairment, metabolic acidosis and DIC. This in turn leads to severe haemorrhage causing the haematocrit to decrease in severe shock.
- Instead of leucopenia, usually seen during this phase of dengue, leucocytosis may occur in patients with severe bleeding.

- Severe organ impairment such as severe hepatitis, encephalitis, myocarditis and severe bleeding may also develop without obvious plasma leakage or shock.
- Those who improve after defervescence are said to have non-severe dengue.
- Cases of dengue with warning signs usually recover with early rehydration. However, some cases will deteriorate to severe dengue.

Recovery Phase

- If the patient survives the 24–48 hours critical phase, a gradual reabsorption of extravascular fluid takes place in the following 48–72 hours.
- General well-being improves appetite returns, gastrointestinal symptoms abate, haemodynamic status stabilises and diuresis ensues.
- Some patients may have a rash of "isles of white in the sea of red".
- Some patients may experience pruritus, particularly on hands and feet.
- Bradycardia and ECG changes are common during this stage.
- The haematocrit stabilises or may be lower due to dilutional effect of reabsorbed fluid.
- White blood cell count usually starts to rise soon after defervescence but recovery of platelet count is typically later than that of white blood cell count.
- Respiratory distress from massive pleural effusion and ascites will occur at any time if excessive intravenous fluids have been administered.

Severe Dengue

- Defined by one or more of the following:
  1. Plasma leakage that may lead to shock (dengue shock) and/or fluid accumulation, with or without respiratory distress.
  2. Severe bleeding.
  3. Severe organ impairment.
- Increasing vascular permeability results in shock. It usually takes place around defervescence, usually on day 4 or 5 (range days 3–7) of illness, preceded by warning signs.
- During the initial stage of shock, compensatory mechanisms produce tachycardia and peripheral vasoconstriction with reduced skin perfusion, resulting in cold extremities and delayed capillary refill time. Diastolic pressure rises towards the systolic pressure and the pulse pressure narrows (≤20 mmHg) as the peripheral vascular resistance increases.
- Patients in dengue shock often remain conscious and lucid.
- Later, patient decompensates and both systolic and diastolic pressures disappear abruptly.
- Prolonged hypotensive shock, may lead to multiorgan failure.
- Hypotension is usually associated with major bleeding as shock in combination with thrombocytopenia, hypoxia and acidosis which can lead to DIC.
- Unusual manifestations include acute liver failure, encephalopathy and cardiomyopathy.
- Most deaths from dengue occur in patients with profound shock, particularly if it is complicated by fluid overload.

Severe Dengue—Summary

Should be considered if a patient from an area of dengue risk presents with fever of 2–7 days plus any of the following features:
- Evidence of plasma leakage
  - High or progressively rising haematocrit
  - Pleural effusions or ascites
  - Circulatory compromise or shock (tachycardia, cold and clammy extremities, capillary refill time >3 seconds, weak or undetectable pulse, narrow pulse pressure or in late shock, unrecordable blood pressure)
- Significant bleeding
- Altered level of consciousness (lethargy or restlessness, coma, convulsions)
- Severe gastrointestinal involvement (persistent vomiting, increasing or intense abdominal pain, jaundice)
- Severe organ impairment (acute liver failure, acute renal failure, encephalopathy or encephalitis, cardiomyopathy)

Diagnosis

- Leucopenia, thrombocytopenia and elevated liver enzymes.
- Isolation of virus from the blood (within first 5 days of onset of clinical features).
- Serum NS1 antigen is highly specific and is positive early in the course of illness.
- Molecular methods like RT-PCR or nucleic acid sequence based amplification (NASBA) to detect viral RNA.
- Rising viral antibody titres (start after 5 days of onset).
- In patients with severe dengue, chest radiograph to look for pleural effusion and ultrasound abdomen for ascites and gall bladder wall thickening.

Overview of Management

- At the first contact, patients should be rapidly screened in order to identify those with severe dengue (who require immediate emergency treatment to avert death), those with warning signs (who should be given priority while waiting in the queue so that they can be assessed and treated without delay) and nonurgent cases. Therefore, following should be done at the first level of healthcare:
  - Recognising that the febrile patient could have dengue
  - Managing patients in early febrile phase of dengue
  - Recognising early stage of plasma leakage or critical phase and initiating fluid therapy
  - Recognising patients with warning signs who need to be referred for admission and/or intravenous fluid therapy to a secondary healthcare facility
  - Recognising and managing severe plasma leakage and shock, severe bleeding and severe organ impairment promptly and adequately.
- During the early febrile phase, it is often not possible to predict clinically whether a patient with dengue will progress to severe disease. Therefore, patients should have daily outpatient healthcare assessments for disease progression with careful checking for manifestations of severe dengue and warning signs.

Stepwise Management

Step I—Overall Assessment

History	Examination	Investigations
• Date of onset of fever/illness • Quantity of oral intake • Warning signs • Diarrhoea • Change in mental state, seizure, dizziness • Urine output • Coexisting conditions	• Mental state • Hydration status • Haemodynamic status • Tachypnoea, acidotic breathing • Pleural effusion • Abdominal tenderness, hepatomegaly, ascites • Rash and bleeding manifestations • Tourniquet test	• Full blood count • Haematocrit (in early febrile phase, establishes baseline haematocrit) (decreasing white blood cell count makes dengue very likely; rapid decrease in platelet count in parallel with a rising haematocrit compared to the baseline is suggestive of progress to the plasma leakage/critical phase of the disease)

Step II—Diagnosis, Assessment of Disease Phase and Severity

- On the basis of step I, determine whether the disease is likely to be dengue, which phase it is in (febrile, critical or recovery), whether there are warning signs, the hydration and haemodynamic status of the patient and whether the patient requires admission.

Step III—Treatment

- Depending on the clinical manifestations and other circumstances, patients may be sent home (Group A), be referred for in hospital management (Group B) or require emergency treatment and urgent referral (Group C).

Treatment of Group A Patients

- These are patients who are able to tolerate adequate volumes of oral fluids and pass urine at least once every 6 hours, and do not have any of the warning signs, particularly when fever subsides.
- These patients should be reviewed daily for disease progression (decreasing white blood cell count, defervescence and warning signs) until they are out of the critical period.

- Those with stable haematocrit can be sent home and are advised to return immediately if they develop any of the warning signs. They are advised to adhere to the following action plan:
  - Oral intake of oral rehydration solution, fruit juice and other fluids containing electrolytes and sugar to replace losses from fever and vomiting.
  - Paracetamol for high fever if patient is uncomfortable.
  - Tepid sponging bath if fever is high.
  - Avoid use of NSAIDs as these drugs may aggravate gastritis or bleeding. Aspirin may also be associated with Reye's syndrome.
  - To be brought to hospital immediately if any of the following occur: No clinical improvement, deterioration around the time of defervescence, severe abdominal pain, persistent vomiting, cold and clammy extremities, lethargy or restlessness, bleeding (e.g. black stools or coffee-ground vomiting), not passing urine for more than 4–6 hours.
- Patients should be monitored daily for temperature pattern, volume of fluid intake, urine output, warning signs, signs of plasma leakage and bleeding, haematocrit and white blood cell and platelet counts.

Calculation of Oral Rehydration Fluids Using Weight

Body weight (kg)	ORS to be given
>3–10	100 mL/kg/day
>10–20	75 mL/kg/day
>20–30	50–60 mL/kg/day
>30–60	40–50 mL/kg/day

Treatment of Group B Patients

- These patients should be referred for in hospital management. These include patients with warning signs, those with coexisting conditions that may make dengue or its management more complicated (such as pregnancy, infancy, old age, obesity, diabetes mellitus, renal failure and chronic haemolytic diseases) and those with certain social circumstances (such as living alone, or living far from a health facility without reliable means of transport).
- If a patient has dengue with warning signs, action plan should be as follows:
  - Obtain a reference haematocrit before fluid therapy
  - Give only isotonic solutions such as normal saline or Ringer's lactate
  - Start with 5–7 mL/kg/hour for 1–2 hours, then reduce to 3–5 mL/kg/hour for 2–4 hours, and then reduce to 2–3 mL/kg/hour or less according to the clinical response
  - Re-assess clinical status and repeat haematocrit
  - If haematocrit remains the same or rises only minimally, continue with the same rate (2–3 mL/kg/hour) for another 2–4 hours
  - If vital signs are worsening and haematocrit is rising rapidly, increase rate to 5–10 mL/kg/hour for 1–2 hours
  - Re-assess clinical status, repeat haematocrit and review fluid infusion rates accordingly
  - Give minimum intravenous fluid volume required to maintain good perfusion and urine output of about 0.5 mL/kg/hour.
  - Intravenous fluids are usually needed for only 24–48 hours
  - Reduce intravenous fluids gradually when rate of plasma leakage decreases towards the end of critical phase, as indicated by urine output and/or oral fluid intake, or haematocrit decreasing below the baseline value in a stable patient.

Maintenance of Intravenous Fluids

- Normal maintenance fluid per hour can be calculated on the basis of the following formula:
  - 4 mL/kg/hour for first 10 kg ideal body weight
  - +2 mL/kg/hour for next 10 kg ideal body weight
  - +1 mL/kg/hour for subsequent kg ideal body weight

Treatment of Group C Patients

- Patients with severe dengue require emergency treatment and urgent referral when they are in the critical phase of disease.
- Plasma losses should be replaced immediately and rapidly with isotonic crystalloid solution or, in the case of hypotensive shock, colloid solutions.
- If possible, obtain haematocrit levels before and after fluid resuscitation.
- The action plan for treating patients with compensated shock is as follows:
  - Start intravenous fluid resuscitation with isotonic crystalloid solutions at 5–10 mL/kg/hour over 1 hour. Then reassess the patient's condition (vital signs, capillary refill time, haematocrit and urine output).

- If patient's condition improves, intravenous fluids should be gradually reduced to 5–7 mL/kg/hour for 1–2 hours, then to 3–5 mL/kg/hour for 2–4 hours, then to 2–3 mL/kg/hour and then reduced further.
- If vital signs are still unstable check haematocrit after the first bolus. If haematocrit increases or is still high (>50%), repeat a second bolus of crystalloid solution at 10–20 mL/kg/hour for 1 hour. After this second bolus, if there is improvement, reduce the rate to 7–10 mL/kg/hour for 1–2 hours, and then continue to reduce as above. If haematocrit decreases compared to the initial reference haematocrit (<40% in children and adult females, <45% in adult males), this indicates bleeding and the need to crossmatch and transfuse blood as soon as possible.
- Further boluses of crystalloid or colloidal solutions may need to be given during the next 24–48 hours.
- The action plan for patients with hypotensive shock is as follows:
  - Initiate intravenous fluid resuscitation with crystalloid or colloid solution at 20 mL/kg as a bolus given over 15 minutes.
  - If patient's condition improves, give a crystalloid/colloid infusion of 10 mL/kg/hour for 1 hour. Then continue with crystalloid infusion and gradually reduce to 5–7 mL/kg/hour for 1–2 hours, then to 3–5 mL/kg/hour for 2–4 hours, and then to 2–3 mL/kg/hour or less, which can be maintained for up to 24–48 hours.
  - If vital signs are still unstable, review haematocrit obtained before the first bolus. If haematocrit was low, this indicates bleeding and the need to transfuse blood as soon as possible.
  - If haematocrit was high compared to baseline value, give intravenous colloid at 10–20 mL/kg as a second bolus over 30 minutes to 1 hour. After second bolus, reassess patient. If condition improves, reduce the rate to 7–10 mL/kg/hour for 1–2 hours, then change back to crystalloid solution and reduce the rate of infusion as mentioned above.
  - If condition is still unstable, repeat haematocrit after second bolus. If haematocrit decreases compared to the previous value, this indicates bleeding and the need to transfuse blood. If haematocrit increases compared to previous value, continue colloid solutions at 10–20 mL/kg as a third bolus over 1 hour.
  - A decrease in haematocrit together with stable haemodynamic status and adequate urine output indicates haemodilution; in this case intravenous fluids must be discontinued immediately to avoid pulmonary oedema.
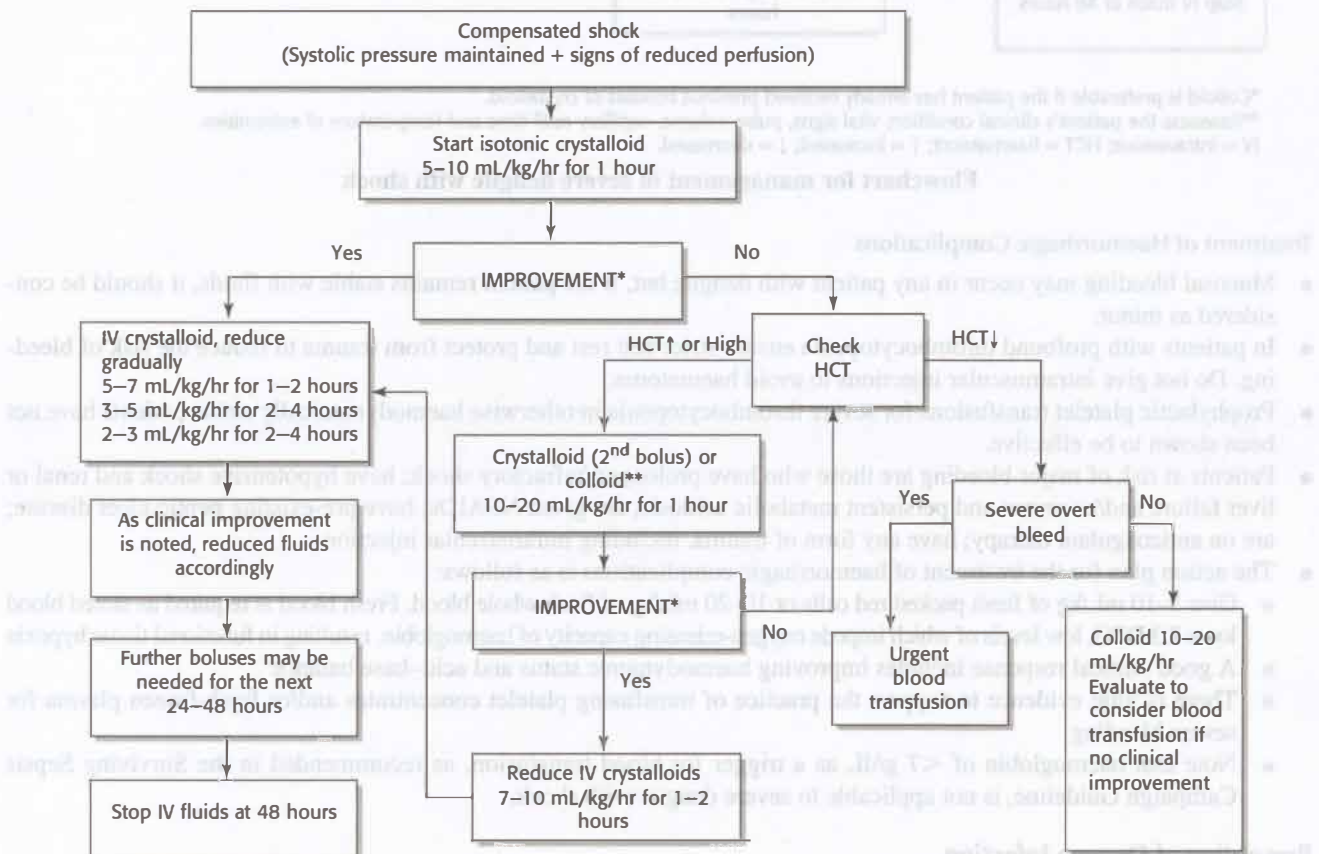
*Reassess the patient's clinical condition, vital signs, pulse volume, capillary refill time and temperature of extremities.
**Colloid is preferable if the patient has already received previous boluses of crystalloid.
-IV: intravenous, HCT: haematocrit, ↑: increased, ↓: decreased.

Flowchart for management of severe dengue with compensated shock

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┌──────────────────────────────────────────────┐
│            Hypotensive shock                   │
│  Try to obtain an HCT level before fluid       │
│              resuscitation                     │
└──────────────────────────────────────────────┘
                     │
                     ▼
┌──────────────────────────────────────────────┐
│      Start isotonic crystalloid or            │
│              colloid*                          │
└──────────────────────────────────────────────┘
                     │
       Yes ┌─────────┴──────────┐ No
           │    IMPROVEMENT*     │
           └────────────────────┘
```

HCT↑ or High — Check HCT — HCT↓

IV crystalloid or colloid
10 mL/kg/hr for 1 hour

IV crystalloid, reduce gradually
5–7 mL/kg/hr for 1–2 hours
3–5 mL/kg/hr for 2–4 hours
2–3 mL/kg/hr for 2–4 hours

IV Crystalloid/colloid*
(2nd bolus)
10 mL/kg/hr for 30–60 min

Severe overt bleed — Yes / No

IMPROVEMENT**

Urgent blood transfusion

Colloid 10–20 mL/kg/hr
Evaluate to consider blood transfusion if no clinical improvement

As clinical improvement is noted, reduced fluids accordingly

Reduce IV crystalloids
7–10 mL/kg/hr for 1–2 hours

Stop IV fluids at 48 hours

*Colloid is preferable if the patient has already received previous boluses of crystalloid.
**Reassess the patient's clinical condition, vital signs, pulse volume, capillary refill time and temperature of extremities.
IV = intravenous; HCT = haematocrit; ↑ = increased; ↓ = decreased.

Flowchart for management of severe dengue with shock

Treatment of Haemorrhagic Complications

- Mucosal bleeding may occur in any patient with dengue but, if the patient remains stable with fluids, it should be considered as minor.
- In patients with profound thrombocytopenia ensure strict bed rest and protect from trauma to reduce the risk of bleeding. Do not give intramuscular injections to avoid haematoma.
- Prophylactic platelet transfusions for severe thrombocytopenia in otherwise haemodynamically stable patients have not been shown to be effective.
- Patients at risk of major bleeding are those who have prolonged/refractory shock; have hypotensive shock and renal or liver failure and/or severe and persistent metabolic acidosis; are given NSAIDs; have pre-existing peptic ulcer disease; are on anticoagulant therapy; have any form of trauma, including intramuscular injection.
- The action plan for the treatment of haemorrhagic complications is as follows:
  - Give 5–10 mL/kg of fresh packed red cells or 10–20 mL/kg of fresh whole blood. Fresh blood is required as stored blood loses 2,3 DPG, low levels of which impede oxygen-releasing capacity of haemoglobin, resulting in functional tissue hypoxia
  - A good clinical response includes improving haemodynamic status and acid–base balance
  - There is little evidence to support the practice of transfusing platelet concentrates and/or fresh-frozen plasma for severe bleeding
  - Note that haemoglobin of <7 g/dL as a trigger for blood transfusion, as recommended in the Surviving Sepsis Campaign Guideline, is not applicable to severe dengue with shock.

Prevention of Dengue Infection

- Preventive measures are directed towards elimination of adult mosquitoes and their larvae.
- During epidemics, aerial spraying/fogging with malathion is recommended for control of adult mosquitoes.
- Mosquito repellants to prevent bites.
- Covering body with full clothes again to prevent bites.

- Larval control measures include source reduction and use of larvicides. As *Aedes aegypti* mosquitoes breed in and around human dwellings and flourish in fresh water, stagnation of water in the coolers, flower pots, bathroom, kitchen, terrace, lawn and other open places should be avoided.
- Another larval control measure is introduction of larvivorous fish, namely *Gambusia* in water tanks and other water sources.
- Currently there is no vaccine or antiviral drug against dengue viral infections.

Q. Give a brief account of chikungunya.

- Chikungunya is a viral fever caused by an alphavirus that is spread by bites from *Aedes aegypti* mosquitoes. Humans are the major reservoir of chikungunya virus. Mosquitoes usually transmit the disease by biting an infected person and then biting someone else. An infected person cannot spread the infection directly to other persons. *Aedes aegypti* mosquitoes bite during the daytime.
- In Swahili (an African dialect), chikungunya means "that bends up" in reference to the stooped posture developed as a result of the arthritic symptoms of the disease.
- Primarily seen in Tamil Nadu, Karnataka, Kerala, Andhra Pradesh and also in Rajasthan, Gujarat and Madhya Pradesh. Increasing number of cases are being reported from northern India including Delhi.
- Chikungunya is generally not fatal. However, in 2005–2006 outbreak in India, more than 200 deaths were associated with chikungunya. These were related to CNS involvement and fulminant hepatitis.
- Incubation period varies from 1 to 12 days.

Clinical Features

- The symptoms of chikungunya include fever, a maculopapular rash usually involving the limbs and trunk and arthralgia or arthritis affecting multiple joints that can be debilitating.
- Shortly after onset of fever, patients develop severe, often debilitating and migrating polyarthralgias. The joint pains are usually symmetric and occur most commonly in wrists, elbows, fingers, knees, and ankles but can also affect more proximal joints. Swelling of joints due to tenosynovitis can be seen in some cases.
- Skin involvement is present in about 40–50% of cases and consists of a pruritic maculopapular rash predominating on the thorax, facial oedema, a bullous rash with pronounced sloughing (mainly in children) and localised petechiae.
- Other symptoms include headache, conjunctival injection and slight photophobia.
- Bleeding from skin (petechiae) and epistaxis may occur in some patients but bleeding from internal organs is unusual. Some patients may develop pedal oedema.
- The fever usually lasts for 2–5 days and abruptly comes down. Other symptoms, particularly joint pains, headache and an extreme degree of prostration last for a variable period, usually for about 7–10 days. However, in some patients, joint pains may last for as long as 6 months or may persist for several years. This is more common in elderly patients.

Diagnosis

- Thrombocytopenia may occur but is uncommon.
- Diagnosis is based on demonstrating antibodies using ELISA method.
- In early stages, viral isolation confirms the diagnosis.
- Molecular methods include RT-PCR to detect structural genes in the blood sample.

Treatment

- The treatment is symptomatic as there is no specific treatment for chikungunya. For arthralgias and arthritis, paracetamol, ibuprofen, diclofenac or naproxen may be used. Rest is also important to reduce morbidity.
- Hydroxychloroquine (200 mg once or twice a day) may be tried in patients with prolonged symptoms of joint pains.

Prevention

- It is on similar lines as that for dengue infection.

Q. Give a brief account of Japanese encephalitis.

- It is a zoonotic disease maintaining Japanese encephalitis virus in nature by bird–mosquito–bird; and pig–mosquito–pig cycles.
- It is an arboviral infection transmitted by the bites of infected culicine mosquitoes (*Culex tritaeniorhynchus*) that have fed on infected animals (pigs) or birds.
- The disease is particularly common in areas where irrigated rice fields are present.
- Bihar, Uttar Pradesh, Assam, Andhra Pradesh, Karnataka, Tamil Nadu, West Bengal and Orissa are major states of India where Japanese encephalitis is endemic.

Clinical Features

- Incubation period is 6–8 days after the bite.
- In endemic areas, the highest age-specific attack rates occur in children of 3 to 15 years of age because of high background immunity in older individuals.
- The illness may present as encephalitis, meningitis or only febrile headache.
- Following incubation period a prodrome of fever, headache, nausea, diarrhoea, vomiting and myalgia occurs lasting for few days (1–5 days) followed by irritability, altered behaviour, convulsions and coma.
- The patient may develop difficulty of speech and other neurological deficits like ocular palsies, hemiplegia, quadriplegia and extrapyramidal signs in the form of rigidity, dystonia, choreoathetosis and coarse tremors.

Diagnosis

- Laboratory abnormalities include leucocytosis with neutrophilia.
- CSF shows raised pressure, cell count and proteins. Neutrophils may predominate in early CSF samples but a lymphocytic pleocytosis is typical. CSF protein is moderately elevated in about 50% of cases.
- Serological tests detect antibodies to viral antigens and include virus neutralisation test, haemagglutination inhibition and complement fixation. A significant rise in titre should be seen with paired samples from the acute and convalescent stages. An IgM-capture ELISA may be useful.
- Viral antigens can be detected in CSF by indirect immunofluorescence assay (IFA). Viral nucleic acid can be analysed by RT-PCR.
- Virus isolation can be done from CSF.
- Persistent EEG abnormalities are commonly seen, particularly in children.
- MRI scans of brain reveal low density areas and abnormal signal intensities in the thalamus and basal ganglia.

Treatment

- Treatment is entirely symptomatic and includes control of fever, raised intracranial tension and convulsions.

Prevention

- Reduction of breeding source of mosquitoes includes water management system, intermittent irrigation and using "neem" products as fertilisers.
- Reduction in man-mosquito contact by various measures including mosquito repellants, pyrethroid impregnated curtains and periodical aerial sprays.
- Several vaccines are in use: purified, formalin-inactivated mouse-brain derived, cell-culture derived inactivated and cell-culture derived live attenuated. Formalin-inactivated vaccine purified from mouse brain requires three doses (0, 7 and 30 days).

Q. Discuss the clinical manifestations, complications, diagnosis and management of diphtheria.

- Diphtheria is caused by *Corynebacterium diphtheriae*, which is a Gram-positive rod with a Chinese letter configuration on Albert's staining. It produces a powerful exotoxin that damages the heart muscle and the nervous system.
- The disease is transmitted by droplet infection from active cases or carriers.
- The incubation period is about 1–7 days.

Clinical Features

- The usual presenting manifestations are fever and sore throat.
- The diagnostic feature is the "wash leather", elevated greyish-green membrane on the tonsils, with a surrounding area of inflammation (membranous tonsillitis). The membrane is firm and adherent.
- There may be swelling of the neck ("bull-neck" appearance) and tender enlargement of cervical lymph nodes.
- Nasal diphtheria is restricted to the nasal mucosa and is characterised by nasal discharge, which is often blood tinged.
- In pharyngeal diphtheria, the diphtheritic membranes are firmly attached to the tonsils or pharynx or both. Later, the soft and hard palates too become covered. In severe cases, there may be accompanying cervical lymphadenopathy and marked oedema of submandibular areas giving rise to the characteristic "bull-neck" appearance (malignant diphtheria).
- In laryngeal diphtheria, there is involvement of the larynx as a result of extension of the diphtheritic membrane from pharynx. There is a husky voice and a high-pitched cough.

- In cutaneous diphtheria, there are round, deep, "punchedout" ulcers covered by a grey-yellow or grey-brown membrane. It occurs in individuals with poor hygiene and with burns.

Complications

- Extension of the membrane into larynx and trachea leads to laryngeal obstruction and bronchopulmonary diphtheria.
- Myocarditis can result in arrhythmias, cardiac failure and ECG changes. It often occurs weeks after initial episode of diphtheria.
- Peripheral neuropathy can occur in a "glove and stocking" distribution.
- Bulbar paralysis results in III, VI, VII, IX and X cranial nerve palsies and diaphragmatic paralysis.
- Encephalitis can occur rarely.

Diagnosis

- The diagnosis is based on the demonstration of the characteristic diphtheritic membrane. However, a variety of other conditions can also cause membranes ("pseudomembranes"). These include infectious mononucleosis, streptococcal pharyngitis, viral exudative pharyngitis, fusospirochaetal infections and acute pharyngeal candidiasis.
- Demonstration of the organisms on methylene blue stained preparations.
- Culture of the organism on Loeffler's medium.
- Detection of toxin by rapid enzyme immunoassay or PCR.

Management

- Isolation and strict bed rest.
- Antidiphtheritic toxin should be given as early in the course of diphtheria as possible. A delay in administration can be dangerous because toxin once fixed to the tissues can no longer be neutralised. A dose of 4000–8000 units is given intramuscularly for mild disease, 16,000–32,000 units intramuscularly for moderately severe disease and up to 100,000 units for very severe disease. Antidiphtheritic serum can cause two types of reactions, an immediate anaphylactic reaction and a delayed serum sickness-like reaction. The immediate anaphylactic reaction should be treated with adrenaline and an antihistamine.
- Benzylpenicillin is given at a dose of 600,000 units 6 hourly intravenously for 7 days to eradicate the organism. Patients allergic to penicillin can be treated with erythromycin.
- Tracheostomy may become necessary for respiratory distress.
- Close contacts should be protected by erythromycin prophylaxis and immunisation.
- Vaccines include DPT (diphtheria, pertussis, tetanus toxins), DT (diphtheria, tetanus toxins) and Td (tetanus, reduced diphtheria toxins).

Q. Explain briefly about anthrax.

Q. Describe cutaneous anthrax and malignant pustule.

Q. Write a short note on inhalation anthrax and wool sorter's disease.

- Anthrax is a zoonotic disease caused by inhaling or ingesting the spores of *Bacillus anthracis*. In males, anthrax is an occupational disease of farmers, butchers and dealers in wool and bone meal. It is an important bioterrorism threat.

Clinical Manifestations

- Cutaneous anthrax results from inoculation of spores subcutaneously often as a result of contact with infected animals or animal products. Cuts or abrasions increase susceptibility to cutaneous infection. The lesion begins as an itching papule that enlarges to form a vesicle. The vesicle is filled with sero-sanguineous fluid and is surrounded by gross oedema ("malignant pustule"). The vesicle dries to form a thick black "eschar" surrounded by blebs. Systemic symptoms including fever, malaise and headache can occur.
- Inhalation anthrax results from inhalation of the spores into the lung leading to "wool sorter's disease". Bioterrorism-related anthrax also occurs due to inhalation of spores. The incubation period is 1–11 days. The disease is characterised by a haemorrhagic bronchopneumonia.
- Meningeal anthrax manifests as fulminant meningitis.
- Intestinal anthrax manifests as gastroenteritis that is at times fatal.

Clinical Features of Inhalational Anthrax

First stage of anthrax	Second stage of anthrax

• Insidious onset of:
  • Malaise
  • Low-grade fever
  • Myalgias
  • Mild cough
  • Retrosternal heaviness
 	
• Lasts for 1–4 days
	• Rapid deterioration with:
	  • Haemoptysis
	  • Acute dyspnoea
	  • Cyanosis
	  • Diaphoresis
	  • Fever
	  • Shock
	  • Meningitis, coma
	
	• Chest X-ray
	  • Mediastinal widening
	  • Pleural effusion

Diagnosis

- A stained smear of fluid taken from the edge of a malignant pustule may demonstrate the organism.
- The organism may also be isolated from stools, laryngeal secretions, sputum and CSF.
- *Bacillus anthracis* may be cultured in mice, rabbits or guinea pigs.
- Chest X-ray showing mediastinal widening, bronchopneumonia and pleural effusion (often haemorrhagic).

Treatment

- The drug of choice for anthrax is penicillin. Dose of penicillin G is 4 million units every 4 hourly in adults and 50,000 units/kg every 6 hourly in children. The organism is also sensitive to ciprofloxacin, tetracycline or doxycycline. Duration of treatment is 2 weeks.
- In anthrax related to bioterrorism, ciprofloxacin is the drug of choice as some strains of bacteria may be resistant to penicillin. Dose is 400 mg ciprofloxacin BID intravenously. Once the patient stabilises, ciprofloxacin can be given orally in a dose of 500 mg BID. Duration of treatment is 60 days.

Prevention

- Prevention of disease in persons exposed to the spores (post-exposure prophylaxis) includes the use of ciprofloxacin (500 mg BID) or doxycycline (100 mg BID) for 60 days.
- Raxibacumab, a human IgG1 gamma monoclonal antibody directed against protective antigen is useful for prevention of inhalation anthrax when alternative preventive therapies are not available or are not appropriate.
- Prevention of anthrax involves vaccination of animals and persons at risk.

Q. Briefly outline the clinical features, treatment and prophylaxis of smallpox.

- The last reported case of smallpox occurred in 1977. WHO declared world free of smallpox in 1980.
- Deliberate introduction of highly contagious smallpox virus via aerosolisation could cause an epidemic of this deadly disease in a few days.
- Caused by Variola virus that belongs to the orthopoxvirus genus; the genus also includes monkeypox, vaccinia, cowpox and other viruses. The two variants of variola virus are variola major and variola minor. Variola minor is less virulent than variola major.
- Smallpox is acquired through exposure of the respiratory or oropharyngeal mucosa to viable virions through contaminated aerosols, lesional tissue, body fluids or fomites.

Clinical Features

- Incubation period is 12–14 days during which there is viral proliferation within the lymph nodes and subsequent dissemination, thereby seeding other lymphoid tissues throughout the body.
- The period from the development of the mucosal rash up to the 10th day of the cutaneous rash, represents the stage at which the disease is most contagious. However, the patient remains contagious till scabs fall off.
- The infection presents abruptly with high fever, headache, backache and malaise.
- Within 2–3 days, the patient develops typical maculopapular rash on the face, forearms, palms, soles and oral mucosa. The rash then spreads to the trunk and legs. Within 48 hours, this centrifugal rash becomes vesicular. In about 4–10 days, the lesions change into pustules. The lesions are deep-seated (in contrast, chickenpox lesions are more superficial).

- All the lesions are at the same stage of development. In contrast, rash in chickenpox is centripetal in nature and at any time skin lesions at various stages of evolution may be seen. In smallpox eruptions commonly occur on the palms and soles, a highly unusual location for the lesions of chickenpox.
- Within 2–3 weeks, the lesions develop into scabs that detach leaving, at times, scars and hypopigmented lesions.
- Death can occur due to DIC, hypotension and multiorgan failure. When smallpox was prevalent, variola major had a case fatality rate of about 30%, and variola minor a case-fatality rate of less than 1%.
- Uncommon presentations are flat and haemorrhagic types of lesions. Flat smallpox is associated with soft, flat, confluent or semiconfluent lesions. Haemorrhagic smallpox produces widespread haemorrhages into skin and mucous membranes with a very high case fatality rate.

Treatment

- Symptomatic only.

Prophylaxis

- No effective post-exposure therapy is available.

Vaccine

- Vaccine can prevent or reduce the severity of infection if administered within 4 days of exposure. However, most countries do not have adequate stock of smallpox vaccine.
- The vaccine employs another virus of orthopoxvirus genus, vaccinia and is a live attenuated vaccine.

Procedure

- The vaccine is applied to dry skin over the deltoid muscle with a bifurcated needle, which after being submerged in the vaccine suspension and retains approximately 2.5 μL of the solution between the prongs.
- The needle is held roughly perpendicular to the surface of the skin and agitated quickly, penetrating the epithelium and producing a drop of blood when the procedure is performed correctly.
- After the procedure, the vaccine site should be covered promptly with a dry sterile dressing, with care taken not to touch the affected skin, which could potentially transmit vaccinia virions to other body parts or to people who have not yet been immunised.
- Successful vaccination—referred to as a "take"—results in the initial production of an erythematous papule in approximately 3 days. One week after vaccination, the lesion matures into a pustule, eventually crusting over and separating 2–3 weeks later.
- The recipient may experience fever, malaise, lymphadenopathy, and diffuse erythema and swelling over the inoculation site.

Contraindications

- Vaccination is contraindicated in immunosuppressed people, people with a history of eczema, atopic dermatitis or other inflammatory dermatoses, children younger than 1 year and pregnant persons.
- Relative contraindications include household contacts of those who are pregnant, immunosuppressed or who have a history of atopic dermatitis or inflammatory skin disease.

Adverse Effects

- An association between vaccination and occurrence of angina and myocardial infarction has been noted in some patients with underlying cardiac disease.
- Myopericarditis may develop due to inflammation of myocardium and pericardium. Clinical features include chest pain, dyspnoea, electrocardiographic changes and elevated levels of cardiac enzymes. Non-steroidal anti-inflammatory drugs are usually effective in treatment.
- Inadvertent inoculation is the most frequent adverse consequence of smallpox vaccination. Vaccinia may spread to other mucocutaneous areas producing lesions if the patient touches the bare vaccination site or resultant lesion and fails to wash hands immediately. This condition typically resolves without significant morbidity.
- Generalised vaccinia occurs if the vaccinia virus enters the circulation leading to focal or widespread vesicular eruption. Occurs 6-9 days after vaccination and subsides on its own.
- Eczema vaccinatum indicates occurrence of generalised erythema, pruritus and vesicles in patients with active or resolved eczema. It is associated with fever and lymph node enlargement. If a large part of body is involved, dehydration can occur due to fluid exudation. Other complications include secondary infection and septicaemia. The mortality rate may be as high as 40%. Prompt administration of vaccinia immune globulin (VIG) is necessary if this condition is suspected.

- Post-vaccinial encephalopathy and post-vaccinial encephalomyelitis may occur in some persons after vaccination.
  - Post-vaccinial encephalopathy usually occurs in children <2 years of age, generally 6–10 days after vaccination. Post-vaccinial encephalomyelitis occurs in children >2 years, generally occur after 10 days. Symptoms include fever, headache, malaise, changes in mental function, seizures and coma. VIG is not of benefit.
- Progressive vaccinia occurs in immunosuppressed people. It is suspected if the lesion at the vaccination site continues to increase in size 15 days or more after the procedure. As the lesion increases in size, it often shows central crater and is prone to secondary bacterial infection. Blood-borne viral dissemination often results in the development of new lesions in the skin, organs and bones. Treatment of progressive vaccinia involves VIG and rigorous supportive care.

Q. Write a brief note on plague.

- Plague, known as "black death", is caused by *Yersinia pestis*, a Gram-negative, nonmotile bacillus.
- Historically, three plague pandemics have killed more than 200 million people, including the Black Death epidemic in 14th century Europe.
- It remains an enzootic infection of rats and other rodents.
- Plague occurs in sylvatic rats that may then spread among more domestic rat species and finally among humans.
- Three types of plague: Bubonic, septicaemic and pneumonic.
- The most common route of infection in humans is after bite of a plague-infected rat flea. Infection may also occur through direct contact with infected tissues or fluids from sick or dead plague-infected animals, by exposure of humans to respiratory droplets from infected animals, especially cats with plague pneumonia or by laboratory exposure to plague bacteria. Person-to-person spread of bubonic and septicaemic plague but without secondary pneumonia does not occur. Pneumonic plague is highly contagious.
- *Y. pestis* appears to be a good candidate agent for a bioterrorist attack. The use of an aerosolised form of this agent could cause an explosive outbreak of primary plague pneumonia in the exposed population, or alternatively the bacteria could be used to infect the rodent population and precipitate a secondary outbreak in humans living in poor conditions.

Clinical Features

Bubonic Plague

- The bubonic plague presents 2–8 days after exposure. The features include high fever, chills, malaise, vomiting and acutely swollen painful lymph nodes, usually in the groin or axilla. These are called the buboes that are rarely fluctuant or suppurative.
- Other manifestations include apathy, confusion, fright, anxiety, oliguria or anuria, tachycardia and hypotension.
- Without specific treatment, complications are common and include secondary septicaemia, secondary pneumonia and meningitis.
- The mortality rate for untreated bubonic plague is 60%.

Septicaemic Plague

- Septicaemic plague may occur as a complication of untreated bubonic plague or pneumonic plague (secondary septicaemic plague). It can also develop in the absence of obvious signs of any primary disease (primary septicaemic plague).
- Septicaemic plague presents with high fever, chills and malaise, but without any lymph node enlargement. Patients may develop septic shock and DIC with vasculitis, petechiae, purpura and large ecchymoses that can mimic meningococcaemia.
- Gangrene of acral regions, like the tip of the nose or the fingers and toes, due to small artery thrombosis may appear in advanced stages of the disease (Black Death).
- Left untreated, the mortality approaches 100%.

Pneumonic Plague

- Pneumonic plague may occur by primary respiratory infection or as a complication of the bubonic and septicaemic forms of the disease (secondary pneumonia).
- Primary form occurs within 1–6 days of exposure.
- It begins abruptly with intense headache and malaise, high fever, vomiting, abdominal pain, diarrhoea and marked prostration. Chest pain, cough, dyspnoea and haemoptysis develop thereafter.
- Respiratory failure develops quickly with septic shock and mortality is high. Without antibiotics, the disease is fatal in almost all patients within 2 or 3 days.

Diagnosis

- Leucocyte counts >20,000/mm^3 and/or thrombocytopenia in 50% cases.
- Smears from blood, sputum, bubo aspirate and cerebrospinal fluid may be stained with Gram, Giemsa or Wayson's stains to demonstrate bipolar staining coccobacilli (safety pin appearance).

- Cultures of various tissue fluids.
- Serological diagnosis is possible but antibodies may not be detectable when the patient first presents.
- In patients with pneumonic plague chest radiograph shows evidence of multilobar consolidation, cavities or bronchopneumonia.
- Septicaemic plague is often associated with laboratory findings of DIC.

Treatment

- With prompt use of antibiotics, fatality rate decreases below 5% for bubonic plague and below 10% for septicaemic and pneumonic plague.
- Effective medications include streptomycin (15 mg/kg BID), gentamicin (2.5 mg/kg TID), ciprofloxacin (500 mg BID), ofloxacin (400 mg BID), levofloxacin (500 mg OD) and doxycycline (100 mg BID). Total duration of treatment is 10 days.

Prophylaxis

- Prevention of human-to-human transmission from patients with plague pneumonia can be achieved by implementing standard isolation procedures until at least 4 days of antibiotic treatment have been administered. For the other clinical types of the disease, patients should be isolated for the first 48 hours after the initiation of treatment. Healthcare workers should wear high-efficiency respirators.
- Contacts should receive tetracycline (500 mg QID), doxycycline (100 mg BID), ciprofloxacin (500 mg BID), ofloxacin (400 mg BID) or levofloxacin (500 mg OD) for 7 days.

Q. Write a short note on botulism.

Q. What are the clinical uses of botulinum toxin?

- It is caused by toxins (botulinum) produced by *Clostridium botulinum*, an anaerobic, spore-forming bacterium. It is the most potent poison known and is lethal at doses as low as 0.05 μg. There are seven types of toxins labeled as A to G.
- Most cases of botulism result from contaminated food being served undercooked; temperature more than 85°C inactivates the toxin.
- Botulism occurs from absorption of the toxin through a mucosal surface, with intestinal absorption being much more common than lung and wound intoxication.
- After absorption the botulinum toxin blocks the release of acetylcholine at the presynaptic level. This results in blockade at neuromuscular junction, postganglionic parasympathetic terminals and autonomic ganglia.

Classification

- Food-borne botulism occurs due to ingestion of preformed toxin in contaminated food. It is the most common form of botulism.
- Wound botulism develops from toxin produced by infection of a wound.
- Infantile botulism results from ingestion of spores, which on germination in the gut, produce toxin.
- Inhalational botulism may occur due to release of aerosolised spores (bioterrorism).

Clinical Features

- Incubation period varies from 2 hours to 8 days.
- Initial presentation includes gastrointestinal symptoms followed rapidly by involvement of cranial nerves, causing diplopia, dysphagia and dysarthria.
- This is followed by progressive, descending motor paralysis and then, diaphragmatic paralysis and death.
- Parasympathetic dysfunction may occur occasionally, which produces dry mouth, paralytic ileus and dilated, nonreactive pupils.
- Fever is absent and patients are alert and oriented, though mild drowsiness may be present.
- Wound botulism is similar except that GI upset does not occur.
- Infant botulism is characterised by onset of constipation, followed by weakness in sucking, crying or swallowing. This is followed by progressive bulbar and extremity muscle weakness.

Diagnosis

- Diagnosis of botulism is based on clinical features.
- Toxin can be demonstrated in blood (food-borne) or stools (infant botulism).
- Culture for organisms from wound.
- Conditions often confused with botulism include GB syndrome, myasthenia gravis, tick paralysis, diphtheria and hypermagnesaemia.

Treatment

- It includes supportive care with assisted ventilation, prevention of secondary infection and administration of equine heptavalent botulinum antitoxin or human botulinum immune globulin (not available in India).

Clinical Application of Botulinum Toxin

- Type A and B have been approved for clinical use.
- Weakness induced by toxin usually lasts for about 3 months. Hence, further injections at regular intervals are required and the interval varies widely depending on the dose and individual susceptibility.
- Useful in:
  - Blepharospasm
  - Hemifacial spasm
  - Strabismus
  - Cervical dystonia (torticollis) and other dystonias
  - Writer's cramps, tics
  - Spasticity
  - Focal hyperhydrosis
  - Neurogenic bladder
  - Cosmetic (removal of frown lines).
- The obvious adverse effects are due to injection of too high a dose or diffusion of the toxin to unintended sites. This may take the form of excessive weakness in the injected muscles or of weakness in muscles adjacent to injected muscles (e.g. dysphagia or dysphonia after injection of neck muscles).

Q. Describe the aetiology, clinical features, complications, diagnosis and management of whooping cough.

- Whooping cough is caused by *Bordetella pertussis*, a Gram-negative coccobacillus.
- Mode of spread is by droplet infection.
- Incubation period is about 7–14 days.

Clinical Features

- The first stage (catarrhal phase) is characterised by a highly infectious upper respiratory catarrh with rhinitis, conjunctivitis and an unproductive cough. This stage lasts about 1 week.
- The distinctive paroxysmal stage that follows is characterised by severe bouts of coughing. This stage lasts from one to several weeks. Coughing paroxysms are associated with the characteristic whoop and may produce cyanosis. Pertussis is most contagious in the catarrhal and early paroxysmal stages.
- The paroxysmal stage is followed by the stage of convalescence during which slow resolution of whoop occurs, although cough may persist for several weeks to months.
- Atypical presentation includes:
  - Previously vaccinated adolescents and adults may have less severe paroxysmal symptoms.
  - Children who are completely vaccinated have shorter courses of illness than incompletely vaccinated children. Female children older than 3 years may have more severe paroxysms than male children of the same age.

Complications

• Bronchopneumonia	• Convulsions
• Atelectasis	• Conjunctival haemorrhage
• Bronchiectasis	• Ulceration of frenum
• Encephalitis	• Prolapse of rectum

Diagnosis

- Peripheral blood lymphocytosis may be seen in well established cases.
- The diagnosis can be confirmed by the isolation of *Bordetella pertussis*. A polyester swab of the nasopharynx is more effective than a swab of the throat or anterior nostril. The polyester swab should be inserted into the base of a nostril and left in the posterior pharynx for 10 seconds before withdrawing.
- PCR to detect *B. pertussis*.
- Direct fluorescent antibody test.

Management

- Starting antibiotics during catarrhal stage is helpful, but during later stages may not reduce duration of disease, though it is helpful in reducing transmission. Erythromycin for 7–14 days is the recommended treatment. Azithromycin and clarithromycin are equally effective and have lesser side effects than erythromycin. Trimethoprim/sulphamethoxazole has been shown to reduce pertussis transmission and is an alternative treatment for patients who are allergic to macrolides.
- A cough suppressant like methadone can reduce the severity of coughing paroxysms.
- Steroids, antihistamines, β-agonists and immunoglobulins have not been shown to be beneficial.

Prevention

- Patients are considered contagious until 3 weeks after the paroxysmal stage ends if not treated during catarrhal stage. If antibiotics have been given during catarrhal phase, patient is considered infectious until 5 days after starting antibiotics. Therefore, close contacts of patients should receive macrolides, particularly if they are unvaccinated.
- Active immunisation with DPT vaccine is effective in preventing the disease. Immunity begins to decline 4–12 years after vaccination, causing adolescent and adult susceptibility. The vaccine can rarely cause convulsions and neurological damage. Currently approved acellular vaccines produce fewer adverse reactions than whole-cell vaccines and have similar effectiveness. A triple vaccine containing tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) is approved for use in adolescents and adults.

Q. Describe enteric fevers.

Q. Write short notes on typhoid and paratyphoid fevers.

Q. Explain briefly about chronic carrier state in typhoid.

- Enteric fevers include typhoid fever caused by *Salmonella typhi* (also known as *Salmonella enterica* serovar Typhi) and paratyphoid fever caused by *S. paratyphi* A and B (*Salmonella enterica* serovar Paratyphi A, B). A range of clinical syndromes including diarrhoeal disease is caused by a large number of nontyphoidal *Salmonella* serovars; they occasionally can also produce invasive disease.
- Gram-negative, flagellate, non-sporulating and facultative anaerobic bacilli.
- These organisms are transmitted by faecal–oral route, usually by carriers, often food handlers, through the contamination of food, milk or water.
- The incubation period of typhoid fever is about 10–14 days, but that of paratyphoid is somewhat shorter.

Pathogenesis

- The typhoid bacilli reach the small intestine, penetrate the mucosa and enter intestinal lymphatics via Peyer's patches to be carried to the bloodstream. The bacilli are disseminated throughout the body and intracellular multiplication takes place. The organisms re-enter the bloodstream producing bacteraemia when all organs are repeatedly exposed to typhoid bacilli.

Clinical Features

- The disease usually presents with fever associated with headache, malaise and chills. A step-like daily increase in temperature to 40–41°C ("step-ladder" pattern) is seen in some cases. The hallmark of typhoid fever is prolonged, persistent fever, often lasting for 4–8 weeks in untreated patients.
- Early intestinal manifestations include constipation, especially in adults or mild diarrhoea in children, associated with abdominal tenderness.
- Mild hepatosplenomegaly may be present and the liver may be tender.
- There may be bradycardia relative to the height of the fever ("relative bradycardia").
- The characteristic rose spots or "rose-red spots" may be seen on the chest and abdomen during the 1st week. These lesions result from bacterial embolism. They are small, 2–4 mm, pale-red macules that blanch on pressure. They usually last only for 2–3 days. *Salmonella* can be cultured from the biopsy of these lesions.
- Often, by the end of 1st week, constipation is succeeded by diarrhoea and abdominal distension, with tenderness in the right iliac fossa. The stools are characteristically described as "pea-soup" because faeces are loose and greenish in colour.
- By the end of 2nd week, patient may become profoundly ill. By 3rd week, toxaemia increases and patient may pass into coma and die.
- Intestinal complications often occur in the 3rd or 4th week of illness.

Complications of typhoid	
• General	Toxaemia, dehydration, peripheral circulatory failure, DIC
• Gastrointestinal	Perforation of intestine, intestinal haemorrhage
• Neurological	Delirium, psychosis, coma, catatonia, meningitis, encephalopathy, peripheral neuritis, deafness
• Miscellaneous	Myocarditis, endocarditis, pericarditis, pyelonephritis, glomerulonephritis, osteomyelitis, arthritis, periostitis, pneumonia, hepatitis, thrombophlebitis

Diagnosis

- White cell count may show leucopenia with relative lymphocytosis.
- Cultures: The maximum positivity of blood culture is found during the 1st week of illness. Early in the illness, culture of bone marrow aspirate will yield the organism, even after a brief prior antibiotic treatment. Stool and urine cultures become positive in the 3rd week.
- Widal test: This test detects agglutinating antibodies to O, H and Vi antigens of *S. typhi*, and H antigens of *S. paratyphi* A and B. A fourfold rise in antibody titre in paired samples is a good criterion, but of limited practical application.
  - The O antigen is the somatic antigen (lipopolysaccharide cell wall component) of *S. typhi* and is shared by *S. paratyphi A*, *paratyphi B*, other *Salmonella* species and other members of the *Enterobacteriaceae* family. Antibodies against the O antigen are predominantly IgM, rise early in the illness and disappear early. In the absence of recent immunisation a high titre of O antibodies (=1:320) is useful, but not specific for typhoid.
  - The H antigens are flagellar antigens of *Salmonella typhi*, *paratyphi A* and *paratyphi B*. Antibodies to H antigens are both IgM and IgG, rise late in the illness and persist for a longer time. These antibodies also have broad cross-reactivity.
  - The Vi antigen is virulent antigen and Vi antibodies typically rise later, after 3–4 weeks of illness and are of little use in the early diagnosis.
- Other serological tests
  - A dot enzyme immunoassay that detects IgG and IgM antibodies against a 50 KD outer membrane protein distinct from the somatic (O), flagellar (H) or capsular (Vi) antigen of *Salmonella typhi* has a variable specificity and sensitivity.
  - Antigen (Vi) detection using ELISA, counterimmune electrophoresis and coagglutination tests.
- Molecular methods
  - PCR to detect flagellin, somatic gene and Vi gene

Treatment

- General management includes bed rest, isolation and maintenance of nutrition and fluid intake.
- Antibiotic therapy. Several antibiotics are effective in enteric fever. Various regimens are given as:
  - Chloramphenicol at a dose of 3–4 g/day till the fever subsides, followed by 2 g/day, for a total duration of 14 days
  - Amoxycillin 4–6 g/day in four divided doses for 14 days
  - Cotrimoxazole (trimethoprim 640 mg plus sulphamethoxazole 3200 mg) in two divided doses daily for 14 days
  - Ciprofloxacin 500–750 mg twice daily for 14 days
  - Ofloxacin 400–800 mg/day for 14 days
  - Ceftriaxone 75 mg/kg/day for 7–14 days
  - Cefotaxime 50–75 mg/kg/day for 7–14 days
  - Cefixime 400 mg twice a day for 10–14 days
  - Azithromycin 1 g once a day for 5-7 days
  - Aztreonam 50–100 mg/kg/day for 14 days
- Certain strains of *S. typhi*, particularly in India, are resistant to chloramphenicol, amoxycillin and cotrimoxazole. These patients should be treated with ciprofloxacin. These are called multidrug resistant strains.
- Even strains that are sensitive to ciprofloxacin in vitro may not respond to ciprofloxacin treatment. These strains are usually resistant to nalidixic acid when tested in vitro (NARST—nalidixic acid resistant *Salmonella typhi*). These patients require longer duration of treatment with ciprofloxacin or with ceftriaxone.
- With increasing use of quinolones, many strains isolated have shown susceptibility to traditional first-line antimicrobials.
- Corticosteroids. Patients with severe toxaemia, central nervous system manifestations and DIC should be given intravenous dexamethasone 3 mg/kg as a loading dose, followed by 1 mg/kg every 6 hourly for 24 hours.
- The late complications of intestinal perforation and haemorrhage occur in the 3rd or 4th week of illness. The management of these complications depends on the availability of sophisticated medical facilities and clinical state of the patient.

Carrier State in Typhoid

- About 3–5% of patients become long-term asymptomatic carriers. Many carriers give no history of typhoid fever and probably had an undiagnosed mild infection.
- Chronic carriers are generally over 50 years old, are more commonly found in females and often have gall stones. *S. typhi* reside in the gall bladder and even within the interiors of stones. They intermittently reach the lumen of the intestine and are excreted in the stool, thereby contaminating water or food.
- Have an approximately 8-fold excess risk of developing gallbladder carcinoma than noncarriers and an approximately 200-fold excess risk of developing hepatobiliary carcinoma compared with people who have had acute typhoid and have cleared the infection.
- Chronic carrier state should be treated with ciprofloxacin for 4 weeks. Cholecystectomy may be necessary in some patients.

Prevention

- The most important way to prevent typhoid fever is good hygiene, proper sewage disposal and proper water treatment.
- Three vaccines against *S. typhi* infection (do not protect against paratyphoid fever):
  - Heat-killed, phenol-extracted, whole-cell vaccine (for parenteral administration). Due to several adverse reactions, not available at present.
  - Ty21a, a live, attenuated *S. typhi* vaccine containing the *S. typhi* strain Ty21a (oral administration in persons >6 years; one capsule every other day for 3 doses).
  - Vi-polysaccharide (parenteral administration in persons >2 years; single-dose).

Q. What are the causes of food poisoning? Discuss briefly the clinical manifestations, diagnosis and management of food poisoning.

- The term "food poisoning" suggests a food-borne disease outbreak where a cluster of two or more individuals develop similar symptoms following the ingestion of a common food. The most common form of "food poisoning" is gastroenteritis following consumption of food containing preformed toxins or organisms that produce toxin in the gut. It is a likely diagnosis when the onset of gastroenteritis exhibits a strong temporal relationship to a particular meal. (refer to Diseases of the Gastrointestinal Tract)
- The causes of food poisoning are given in the box.

Causes

Infective

- Toxin-induced
  - Preformed toxins: *Staphylococcus aureus, Bacillus cereus*
  - Enterotoxins produced in the intestine: *Vibrio cholerae, E. coli* (enterotoxigenic, ETEC), *Clostridium perfringens, Clostridium difficile*
- Changes in mucosa
  - Mucosal alteration without invasion: Rotavirus, Norwalk agent
  - Invasion of mucosa with destruction: *Shigella, E. coli* (enteroinvasive), *Campylobacter, Yersinia enterocolitica, Salmonella, Entamoeba histolytica, Bacillus anthracis*

Noninfective

- Allergic: Shellfish, strawberries
- Non-allergic: Scrombrotoxin (fish), ciguatoxin (tropical fish), fungi (*Amanita phalloides*), arsenic poisoning

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- Shiga-producing strain of *E. coli* O157:H7 and more recently new strain O104:H4 (reported from Germany) can result in haemolytic–uraemic syndrome in many infected persons including adults.
- Ciguatera fish poisoning occurs after eating reef fish (tropical fish) contaminated with toxins such as ciguatoxin which originate from small marine organisms (dinoflagellates). Dinoflagellates are ingested by herbivorous fish in which ciguatoxin is concentrated as it passes up the food chain to large carnivorous fish and finally to humans. Besides features of acute gastroenteritis occurring within 1–3 hours, neurologic features also develop over next few hours and include paraesthesias, pain in teeth, metallic taste, blurred vision and cold allodynia (touching cold objects produces pain).
- Scrombrotoxin (histamine) poisoning occurs due to ingestion of some fish which have high histidine content e.g. tuna, sardine etc. Histidine is converted into histamine if fish is stored improperly. Features include facial flushing, headache, palpitations, itching, blurred vision, abdominal cramps and diarrhoea. Occasionally, cardiac arrhythmia and hypotension may occur.

Clinical Features and Diagnosis

- Food poisoning presents with vomiting, diarrhoea or both, usually within 48 hours of consumption of the contaminated food or drink. The stools may be bloody and there may be associated crampy abdominal pain and fever.
- Noninfective causes and bacterial toxins that are preformed in the infected food produce symptoms within minutes or hours of a meal, whereas other conditions may not produce symptoms for up to 48 hours.
- Usually, there is a history of simultaneous occurrence of symptoms in more than one member of a household or institution.
- Diagnosis is based on the identification of the specific pathogen by culture of the patient's stool, vomitus or blood or the contaminated food.

Management

- Non-specific therapy includes oral or intravenous replacement of fluid and electrolyte deficits and codeine phosphate or loperamide for controlling diarrhoea (only if the patient does not have fever or blood in the stools). Loperamide should be avoided in young children and elderly persons.
- Antibiotics should not be given routinely, as they are usually ineffective and frequently exacerbate symptoms. However, antibiotic therapy is indicated in selected cases where the specific pathogen is isolated.

Q. Give a brief description about the aetiology, clinical presentation, diagnosis and management of acute bacillary dysentery.

Q. Discuss the aetiology, pathogenesis, clinical features, diagnosis and complications of amoebic dysentery.

Q. Write a short note on amoebic colitis.

- Dysentery is an acute inflammation of the large intestine (colitis) characterised by diarrhoea with blood and mucus in the stools. It is caused by bacillary and amoebic infections.

Bacillary Dysentery

- Bacillary dysentery results from an acute infection of the intestinal tract by one of the three *Shigella* species—*S. dysenteriae*, *S. flexneri* and *S. sonnei*.
- These organisms produce an endotoxin as well as an exotoxin (Shiga toxin). The exotoxin has enterotoxin activity causing intestinal secretion and cytotoxic properties directed against intestinal epithelial cells.

Clinical Features

- *S. sonnei* produces only mild infection. *S. flexneri* infection is usually more severe, while that due to *S. dysenteriae* may be fulminating and cause death within 48 hours.
- Fever and signs of systemic toxicity may be present in severe cases.
- Signs of dehydration and electrolyte disturbances are present in severe cases.
- The dysentery is mild to severe in intensity and is associated with tenesmus and colicky abdominal pain.
- The stools are small in quantity, and contain blood, mucus and purulent exudate with little faecal material.
- There may be tenderness over the colon elicited in the left iliac fossa.
- Bowel sounds are hyperactive.

Complications

- Rectal prolapse.
- Toxic megacolon.
- Colonic perforation.
- Bacteraemia.
- Meningismus, seizures.
- Transient peripheral neuropathy.
- Reiter's syndrome (reactive arthritis) with arthritis, conjunctivitis and urethritis may follow shigellosis.
- Haemolytic–uraemic syndrome, thrombotic thrombocytopenic purpura.

Diagnosis

- Diagnosis depends on the isolation of the organism from stool cultures.
- Sigmoidoscopy shows that the mucosa is red and swollen. The submucous veins are obscured and mucopus is seen on the surface.

- Enzyme immunoassay to detect Shiga toxins in stools.
- PCR for Shigella DNA in stools.

Management

- The fluid and electrolyte deficits should be corrected by intravenous fluids in severe cases.
- Codeine or loperamide may be used to control diarrhoea in adults who do not have dysentery.
- Infections caused by *S. dysenteriae* and *S. flexneri* should be treated with cotrimoxazole or ciprofloxacin. Second-line agents include azithromycin and ceftriaxone.

Amoebic Colitis

- Amoebic colitis can occur in two forms: Amoebic dysentery and non-dysenteric amoebic colitis.

Amoebic Dysentery

Pathogenesis

- Amoebic dysentery results from infection of the large intestine by *Entamoeba histolytica*.
- Caused by ingestion of tetra-nucleated cysts that can remain viable for weeks to months. However, these are destroyed in temperature below −5°C or above 40°C.
- After ingestion (faecal–oral transmission) the cysts undergo further nuclear division and eight trophozoites are released in the terminal ileum. The trophozoites are carried to the large intestine where they produce the characteristic "flask-shaped" amoebic ulcerations. Incubation period is 2–6 weeks.
- Most often, the infection remains subclinical; however, antibody response generally occurs even without local invasion. These asymptomatic patients also need to be treated to prevent transmission to others and occurrence of colitis at a later period.
- A localised granuloma (amoeboma) presenting as a palpable mass in the rectum or causing a filling defect in the colon on radiography is a common complication.
- Amoebae may enter a portal venous radicle and be carried to the liver where they multiply and produce an amoebic liver abscess. They can also travel to lungs and brain.

Clinical Features

- In amoebic dysentery, there is intermittent diarrhoea consisting of one to four, foul-smelling, loose, watery stools that may contain mucus and blood. Flatulence and abdominal cramping are frequent. Fever occurs in some patients.
- Physical examination reveals tender hepatomegaly and tenderness over the caecum (amoebic typhlitis), ascending colon and over the left iliac fossa (amoebic point or Manson–Barr point).

Complications

- Massive haemorrhage.
- Perforation and peritonitis.
- Toxic megacolon in fulminant cases.
- Post-dysenteric colitis.
- Amoebic liver abscess (presents with fever, right upper quadrant pain and intercostal tenderness on right side); abscess may rupture into pleural cavity, pericardial cavity, peritoneal cavity or into the lungs.
- Pleuropulmonary amoebiasis.
- Amoebic pericarditis.
- Cutaneous amoebiasis.
- Rectovaginal fistula.

Diagnosis

- Stool examination: Microscopic examination of a fresh sample of stool may demonstrate the motile trophozoites. They are about 30 microns in diameter, with a clear ectoplasm and a granular endoplasm, and usually contain red blood cells (haematophagous trophozoites). If a fresh stool specimen cannot be examined immediately, it should be preserved with a fixative such as polyvinyl alcohol or kept cool (4°C).
- Sigmoidoscopy: Sigmoidoscopy may reveal the characteristic "flask-shaped" ulcers with normal surrounding mucosa. The aspirated material or scrapings from the ulcer or biopsy of the ulcer may demonstrate the trophozoites.
- Amoebic serology: Serologic tests (indirect haemagglutination test, ELISA or counter-immunoelectrophoresis) can detect antibodies in the blood. These tests are of more use in extraintestinal amoebiasis.

- Chest radiography and ultrasound for amoebic liver abscess.
- Newer methods include detection of *E. histolytica* antigen or DNA in a stool sample.

Non-Dysenteric Amoebic Colitis

- Presents as recurrent bouts of diarrhoea with or without mucus, but no visible blood.
- Stools show *E. histolytica* cysts or non-haematophagous trophozoite (trophozoites with no ingested red blood cells).

Treatment

- Invasive intestinal amoebiasis is treated with metronidazole 800 mg thrice daily for 5 days or tinidazole 2 g daily as a single-dose for 3 days. Other options are secnidazole or ornidazole.
- After treatment, diloxanide furoate should be given at a dose of 500 mg thrice daily for 10 days to eliminate luminal cysts. Alternative agents include iodoquinol, nitazoxanide and paromomycin.

Q. How will you differentiate amoebic dysentery from bacillary dysentery on stool examination?

Features	Amoebic dysentery	Bacillary dysentery
Macroscopic		
• Frequency	6–8 motions a day	Over 10 motions a day
• Amount	Relatively copious	Relatively small
• Odour	Offensive	Odourless
• Nature	Blood and mucus mixed with faeces	Blood and mucus, no faeces
• Colour	Dark red	Bright red
• Reaction	Acidic	Alkaline
• Consistency	Not adherent to the container	Adherent to the container
Microscopic		
• RBC	In clumps	Discrete or in rouleaux
• Pus cells	Scanty	Numerous
• Macrophages	Very few	Large and numerous
• Eosinophils	Present	Scarce
• Parasites	Trophozoites of *E. histolytica*	Nil
• Bacteria	Nil	Motile bacteria
• Charcot–Leyden crystals	Present	Absent

Q. Explain briefly about brucellosis (abortus fever; Malta fever; undulant fever; Mediterranean fever).

- Brucellosis, a zoonotic disease, is an infection caused by one of the four species: *Brucella melitensis* (goats, sheep and camels), *Brucella abortus* (cattle), *Brucella suis* (pigs) and *Brucella canis* (dogs).
- *Brucella* is a Gram-negative organism.
- The natural reservoir of brucellosis is animals. Human infection most commonly results from ingestion of infected animal tissues or milk products or directly through abraded skin. Inhalational route is also seen in some patients. Transmission from human-to-human, particularly mother-to-child, has been described rarely.
- Brucella bacilli interact with neutrophils and tissue macrophages and spread via lymphatics to the regional lymph nodes, especially axillary, cervical and supraclavicular nodes. The organisms can also spread via blood stream to other structures like bone marrow, liver, spleen, bones, endocardium, kidneys and testes. There is formation of non-caseating granulomas in these tissues.

Manifestations

Acute Brucellosis (<2 Months)

- Acute onset in nearly 50% cases.
- Incubation period is 2–3 weeks.
- The onset is acute with fever, malaise, chills, fatigue, weakness, backache and myalgia. Patients are anorectic, lose weight and have cough and arthralgias.
- Fever is classically undulant, although continuous and intermittent patterns are also seen.
- Physical findings include splenomegaly (20% cases), lymphadenopathy (15% cases) and hepatomegaly (10% cases). Sacroiliitis may also occur with tenderness on sacroiliac joints.
- A few patients may manifest with localised brucellosis in the form of osteomyelitis, splenic abscess, epididymo-orchitis, pneumonia, pleural effusion and endocarditis.

Subacute Brucellosis (2–12 Months)

- Similar to acute form, but less severe features.

Chronic Brucellosis (>12 Months)

- Chronic brucellosis is defined as ill health for more than 1 year following onset of brucellosis. These patients may have low-grade fever and neuropsychiatric manifestations. Arthralgia is also common.
- Splenomegaly is often present.
- Other features are those seen with localised features of brucellosis. These are more common than in the acute variety.
- Bone and joint complications are the most frequent complications. These include sacroiliitis, spondylitis, peripheral arthritis, osteomyelitis and bursitis.

Diagnosis

- Brucella can be cultured from blood, bone marrow and other involved tissues. For this, biphasic method of Castaneda that uses both a solid and a liquid medium in the same container is required.
- Brucella agglutination test—A fourfold rise in titre of agglutinating antibody (IgM) may be diagnostic.
- PCR to detect Brucella antigen in blood and tissues.
- Other important tests include ultrasound and CT, bone radiographs and radionuclide scans.

Treatment

- The treatment of choice is doxycycline 100 mg twice a day for 6 weeks plus streptomycin (1 g twice a day) or gentamicin (1.25–2.5 mg/kg twice a day) for 2–3 weeks. An alternative is to give doxycycline plus rifampicin (10–15 mg/kg as one or two doses/day) for 6 weeks though it is slightly inferior to doxycycline plus streptomycin combination. Doxycycline is preferred over tetracycline.
- Seriously ill patients may be given triple therapy with doxycycline, aminoglycoside and rifampicin.
- Spondylitis and endocarditis complications need long treatment courses and possibly surgical treatment.

Q. Write a short note on cholera and cholera sicca.

- Cholera is an acute illness that results from colonization of the small intestine by *Vibrio cholerae*. The disease is characterised by its epidemic occurrence and explosive, severe diarrhoea with rapid depletion of extracellular fluid and electrolytes.
- The major pathogenic strain has a somatic antigen (O1). It is called serogroup O1. It has two biotypes: Classical and El Tor. The El Tor biotype has replaced the classical biotype as the major cause of cholera. Infection with El Tor biotype often causes milder disease, though severe diarrhoea can also occur.
- However, in 1992, a new serogroup O139 (Bengal serogroup) caused an epidemic in India and is still the major cause of cholera in our country. The clinical features are similar to those of O1 serogroup, but the organism may be resistant to cotrimoxazole.

Pathogenesis

- *Vibrio cholerae* produces a powerful enterotoxin that is responsible for the pathophysiologic aberrations in cholera. The enterotoxin stimulates adenylate cyclase of the intestinal epithelial cells resulting in a secretory diarrhoea. There is no demonstrable damage in the intestinal epithelial cells.
- Besides its action on adenylate cyclase, the toxin also enhances intestinal secretion via prostaglandins.
- The pathophysiologic defect in cholera is extracellular fluid depletion with resultant hypotension, metabolic acidosis and hypokalaemia.
- In severe cases, massive fluid loss may lead to hypovolaemic shock and acute tubular necrosis resulting in renal failure.

Clinical Features

- The incubation period is about 12–48 hours.
- Explosive onset of watery diarrhoea without pain or colic follows vomiting (vomiting may be absent). The characteristic "rice-water" stool consists of clear fluid with flecks of mucus. Several litres of isotonic fluid may be lost within hours, leading rapidly to profound shock.
- In extreme cases, there may be signs of severe dehydration. The skin is cold, clammy and wrinkled ("washerwoman" skin) with loss of skin turgor. The blood pressure drops and the pulse becomes rapid and thready.
- Occasionally, a very severe form of the disease occurs in which the loss of fluid into the dilated bowel kills the patient before typical gastrointestinal symptoms appear. This is known as "cholera sicca".

Diagnosis

- "Hanging drop" preparation of the stool demonstrates the characteristic motile organisms (darting motility).
- Culture of the stool or a rectal swab can be used to isolate and identify the organism.
- Immunoassays to detect cholera toxin or *V. cholera* O1 and O139 lipopolysaccharide directly in stool.

Treatment

- Vigorous intravenous fluid and electrolyte therapy should be continued till the patient is haemodynamically stable and vomiting subsides. The ideal solution for intravenous therapy should contain sodium chloride (5 g/L), potassium chloride (1 g/L) and sodium bicarbonate (4 g/L). The initial fluid deficit should be replaced within 3–4 h of presentation. Replacement of ongoing losses is also crucial.
- Patients with severe cholera may require an average of 200–300 mL/kg of isotonic fluids in the first 24 hours.
- Once the patient is haemodynamically stable further deficits may be corrected orally. Previously, oral rehydration solution contained commercial salt (NaCl) 3.5 g/L, potassium chloride (1.5 g/L), sodium bicarbonate (2.5 g/L) and glucose (20 g/L). However, presently, a lower osmolarity solution is recommended in patients with all types of diarrhoea. The composition is sodium chloride (2.6 g/L), potassium chloride (1.5 g/L), trisodium citrate (2.9 g/L) and glucose (13.5 g/L) with an osmolarity of 245 mOsm/L.
- 3 days' treatment with tetracycline 500 mg 6 hourly or cotrimoxazole one double strength tablet daily reduces the duration or excretion of vibrios and the total volume of fluid needed for replacement.
- Single-dose doxycycline (300 mg) and tetracycline (2 g) are also effective.
- Other alternative drugs include ciprofloxacin (1 g as single-dose or 500 mg twice a day for 3 days), azithromycin (1 g as single-dose) erythromycin (250 mg 6 hourly for 3 days) and trimethoprim-sulphamethoxazole.
- Zinc supplementation in children may be helpful in reducing severity of diarrhoea.

Prophylaxis

- Chemoprophylaxis can be given using tetracycline 500 mg twice a day for 3 days.
- Whole-cell killed vaccines are available as oral vaccines.

Q. Discuss the aetiology, clinical features, diagnosis and management of Hansen's disease (leprosy).

Q. Describe lepra reactions and their management.

Q. Write a short note on erythema nodosum leprosum (ENL).

Definition

- Leprosy (Hansen's disease) is a chronic granulomatous disease, primarily affecting the peripheral nerves and secondarily involving the skin. The causative organism is *Mycobacterium leprae*, which is an acid-alcohol-fast bacillus.
- The most important mode of spread of *M. leprae* is by droplets from the sneezes of lepromatous patients, whose nasal mucosa is heavily infected. The organism may enter the body through the nasal mucosa or by inoculation through the skin. Other rare routes include soil transmission and through insect bites.
- Incubation period is generally 2–6 years.

Epidemiology

- Global leprosy prevalence is 0.84 per 10,000 population.
- Two countries, India and Brazil, account for nearly two-thirds of global burden of leprosy.
- In India, prevalence was much higher (3.3 per 10,000 population) in 2003. However, due to consistent efforts, as of April 2014, the figure is 0.68 per 10,000 population (leprosy eliminated). A total of 1.27 lakh new cases were detected during the year 2013–2014. A total of 33 states/union territories have achieved level of leprosy elimination (prevalence <1 per 10,000 population). However, Chhattisgarh, Dadra and Nagar Haveli still have prevalence rate >1 per 10,000 population.
- Goal is to reduce prevalence in every country to below 1 per 10,000 population (elimination of leprosy).

Bacteriological Considerations

- *Mycobacterium leprae* is an acid-alcohol-fast bacillus resembling tubercle bacillus. However, it is less acid and alcohol fast than *Mycobacterium tuberculosis*.
- On Ziehl–Neelsen-stained smears or sections the bacilli are seen singly, in clumps or as globi. Both living and dead bacilli are stained by the Ziehl–Neelsen technique. The living bacilli appear as uniformly stained rods ("solid staining"). The dead bacilli are irregularly stained, either appearing "fragmented" or "granular".
- It appears to survive better at a temperature close to 30°C rather than 37°C. Hence, it affects the skin, peripheral nerves, the mucosa of the upper airways and other tissues such as bone and some viscera.

- *Mycobacterium leprae* can be grown in mice and the armadillo, but not in artificial media. Local multiplication of the organism in the footpads of mice is a useful technique for studies.
- Bacterial index (BI) is the density of bacilli in the smears. It includes both living and dead bacilli.
- Morphological index (MI) is the percentage of living bacilli, calculated after examining 200 red-staining elements lying singly. This is more sensitive index for bacteriological improvement.
- SFG index is based on the appearance of bacilli—"S" for solid, "F" for fragmented and "G" for granular.

Clinicopathologic Classification

- In the early stage, the disease may be indeterminate and may spontaneously remit or develop into overt leprosy.
- The determinate form of the disease may be classified as tuberculoid (TT), borderline or dimorphic, and lepromatous (LL). This forms a spectrum with diminishing host resistance. Resistance is highest in tuberculoid leprosy (TT) and diminishes through borderline spectrum, and is lowest in lepromatous leprosy (LL). The borderline group is further subdivided into borderline tuberculoid (BT), borderline (BB) and borderline lepromatous (BL) classes.

Showing the spectrum of immunity and classification of leprosy
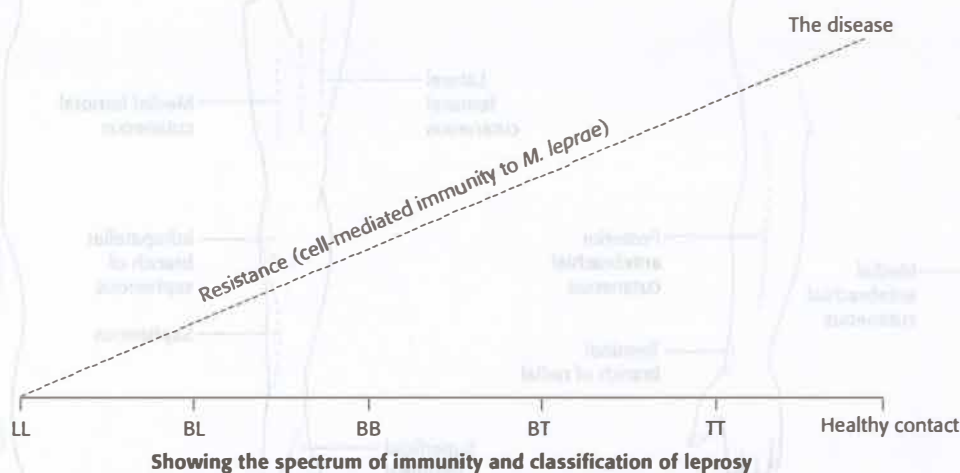
LL = Lepromatous leprosy. BL = Borderline lepromatous leprosy. BB = Borderline leprosy. BT = Borderline tuberculoid leprosy. TT = Tuberculoid leprosy.

- Lepromatous leprosy (LL) is one of the polar forms. This is characterised by extensive, diffuse and bilaterally symmetric skin lesions that contain numerous bacilli. The peripheral nerves are better preserved than in the tuberculoid form.
- Tuberculoid leprosy (TT) is the other polar form. This is characterised by single or few sharply demarcated skin lesions with predominant peripheral nerve involvement. The bacilli are usually absent or difficult to demonstrate.
- Bacilli are present in large numbers in the skin lesions of borderline (BB), borderline lepromatous (BL) and LL. For this reason these three groups are referred to as multibacillary (MB).
- BT, TT and indeterminate (I) classes are grouped together as paucibacillary leprosy (PB).
- An additional classification by the World Health Organisation is based on the number of skin lesions only. People with five or less skin lesions are classified as having paucibacillary (PB) leprosy, while people with six or more skin lesions are classified as having MB leprosy.

Clinical Features

Tuberculoid Leprosy (TT)

- Skin involvement: The early manifestation is a hypopigmented macule that is sharply demarcated and hypoaesthetic. Later, the lesions become larger, and the margins are elevated and circinate or gyrate. The lesions show peripheral spread and central healing. Fully developed lesions are anaesthetic, with loss of sweat glands and hair follicles.
- Nerve involvement: Nerve involvement occurs early and is usually asymmetric. Involved nerves are thickened and palpable. A routine examination should include palpation of the ulnar, peroneal (lateral popliteal) and greater auricular nerves, as they are frequently involved. The other nerves that are involved are depicted in the figure.
- At times, TT may present with only nerve involvement with no skin lesions (neural leprosy or pure neuritic leprosy).
- Sensory nerve involvement results in sensory dysfunctions like glove and stocking anaesthesia (more common in LL), chronic non-healing plantar ulcers, and repeated injuries to hands and feet.
- Motor nerve involvement results in a variety of abnormalities. There is muscle weakness, wasting and later paralysis, followed by contractures.
  - Ulnar nerve—claw hand or "main en griffe".
  - Median nerve—ape hand or "main de singe".

- Lateral popliteal nerve—foot drop.
- Posterior tibial nerve—claw toes or hammer toes.
- Autonomic involvement results in anhidrosis or hyperhidrosis.
- Cranial nerve involvement: Facial nerve (seventh cranial nerve) is commonly involved resulting in facial paralysis, lagophthalmos, exposure keratitis and corneal ulcerations leading to blindness. Trigeminal nerve (fifth cranial nerve) involvement may occur early with loss of corneal reflex.

Sensory nerves of arms

Sensory nerves of legs
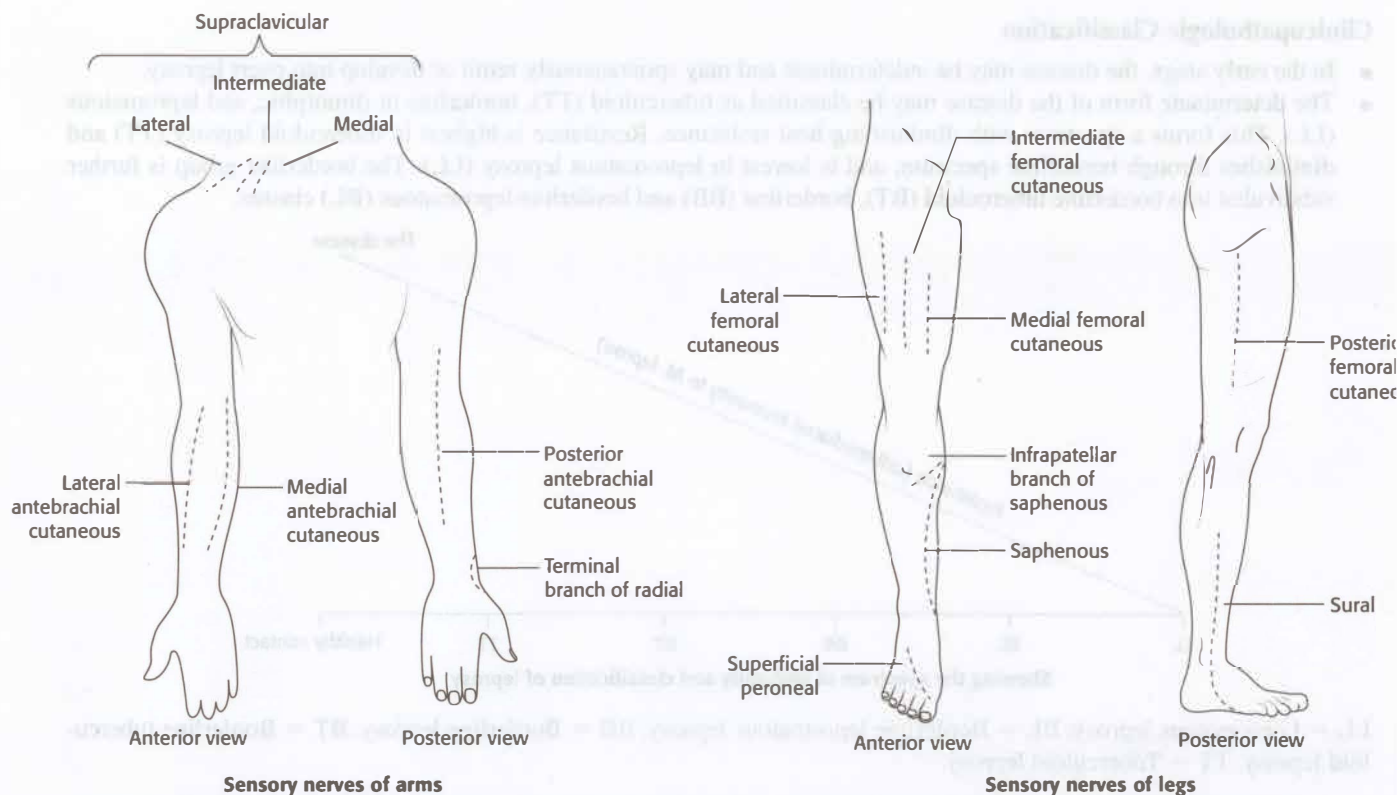
Lepromatous Leprosy (LL)

- Nasal symptoms: These are early symptoms of LL. They include anosmia, nasal stuffiness, crust formation and blood-stained nasal discharge.
- Skin involvement. The skin lesions are macules, nodules, plaques or papules. The macules are often hypopigmented. The borders of the lesions are ill-defined, and the centres indurated, raised and convex ("inverted saucer" appearance). There is also diffuse infiltration between the lesions. The sites of predilection are face (cheeks, nose, eyebrows), ears, wrists, elbows, buttocks and knees. Thickening and nodulation of ears and loss of lateral eyebrows are early manifestations. With advanced disease, the skin of the face and forehead becomes thickened and corrugated ("leonine facies").
- Nerve involvement: Involvement of major nerve trunks is less prominent in LL, but a "glove and stocking" anaesthesia is common in advanced disease. Mononeuritis multiplex can also occur.
- Bone involvement occurs in hands, feet and skull. There is slow atrophy and absorption of distal phalanges leading to shortening of fingers. In the feet, phalanges, metatarsals and tarsal bones are involved. In the skull, there is atrophy of the anterior nasal spine (contributing to nasal collapse) and atrophy of maxillary alveolar process (contributing to loosening and loss of upper incisors). These two skull changes are together called "facies leprosa".
- Other manifestations
  - Bilateral oedema of legs and ankles.
  - Swollen and broad nose, septal perforation and nasal collapse leading to saddle nose.
  - The upper incisor teeth may loosen and fall off.
  - Laryngitis, palatal perforation and hoarseness of voice.
  - Involvement of the anterior chamber of the eye results in keratitis and iridocyclitis.
  - Testicular atrophy, impotence, infertility and gynaecomastia.
  - Painless inguinal and axillary lymph nodal enlargement.
  - Renal amyloidosis, glomerulonephritis, interstitial nephritis and pyelonephritis.

Borderline Leprosy (BB)

- Clinical manifestations of BB are poorly defined. There is a significant overlap in the clinical features of various subtypes.

Reactional States or Lepra Reactions

- The general course of leprosy may be interrupted by two types of reactions. Both forms of reactions can occur in untreated patients, but more often, emerge as complications of chemotherapy.

Reversal Reaction or Downgrading Reaction (Type 1 Lepra Reaction)

- This can complicate all three borderline categories, generally during first few months of treatment.
- Occurs due to a sudden increase in T-cell reactivity to mycobacterial antigens expressed clinically by exacerbation of skin and nerve trunk inflammation, leading to sensory and motor alterations.
- Existing skin lesions develop erythema and swelling and new lesions may appear. The nerves are painful and tender and nerve function may be lost rapidly unless the reaction is treated promptly. Oedema of hands and feet is common.
- When type 1 lepra reaction precedes the initiation of treatment of leprosy, it is called downgrading reaction and the patient becomes more lepromatous histologically. When the reaction occurs after the start of therapy, it is termed reversal reaction; the patient becomes more tuberculoid.

Erythema Nodosum Leprosum (Type 2 Lepra Reaction)

- This occurs in patients with borderline (BL) or LL often during the 2nd year of treatment.
- Occurs due to wide spread immune complexes deposition and overproduction of TNF-α.
- Tender and inflamed subcutaneous nodules develop, usually in crops. Each nodule lasts for a week or two, but new crops may appear. Severe reactions may be accompanied by low-grade fever, lymphadenopathy and arthralgias. In addition, iritis, orchitis, myositis, neuritis and oedema can occur.
- Most people have acute multiple episodes of erythema nodosum leprae (ENL) or chronic ENL. Chronic ENL is defined as an episode lasting for more than six months. This could include single and multiple episodes. Few people experience a single acute episode of ENL.
- After completion of treatment, people may still have episodes of ENL for several years, because they have persisting mycobacterial antigens despite successful antibacterial treatment.

Diagnosis of Leprosy

- Nasal secretions from patients with LL contain numerous bacilli.
- Demonstration of acid-fast bacilli in skin smears made by the scraped incision method is useful in borderline lepromatous and LL. In TT, bacilli are not demonstrable. Smears are made from skin lesions, earlobes and dorsum of the ring or middle finger.
- Involvement of peripheral nerves in a skin biopsy specimen from the affected area is pathognomonic, even in the absence of bacilli.
- Lepromin test: Lepromin is a suspension of dead *M. leprae*. The test is performed like the tuberculin test, but is read after 4 weeks. Positive reactions are obtained in TT, negative responses in LL and negative or weakly positive responses in BB. The test is of limited diagnostic value.
- Hypergammaglobulinaemia is common in LL that can give false positive serological tests (VDRL, rheumatoid factor and antinuclear antibodies).
- IgM antibodies to PGL-1 (phenolic glycolipid-1) are present in 95% of LL but in only 60% of TT. These antibodies may also be present in normal persons.

Treatment

- The main drugs available for the treatment of leprosy are dapsone (100 mg), rifampicin (600 mg), clofazimine (100 mg), ethionamide (500 mg) and thiacetazone (150 mg).
- The side effects of dapsone include haemolysis, agranulocytosis, hepatitis and exfoliative dermatitis.
- The major side effects of clofazimine are restricted to the skin and intestinal tract. They include reddish skin pigmentation, ichthyosis, diarrhoea and cramping abdominal pain.
- Three other drugs—ofloxacin, minocycline and clarithromycin—have also been found to be effective against leprosy.

Multibacillary Leprosy

- Two recommended regimens are given in the information box. The first regimen for multibacillary leprosy (MB) is the ideal, when compliance is good. The second regimen is recommended by the WHO, when the compliance is poor. The duration of treatment is 1 year for multibacillary and 6 months for PB.

Treatment of multibacillary leprosy (MB)

Regimen 1
- Dapsone 2 mg/kg daily, not exceeding 100 mg
- Clofazimine 50 mg daily or 100 mg three times a week
- Rifampicin, 450 mg (for those who are <35 kg) or 600 mg (for those who are <35 kg), on 2 consecutive days a month.

Regimen 2
- Dapsone 100 mg daily (self-administered)
- Clofazimine 50 mg daily (self-administered) plus 300 mg once a month (supervised)
- Rifampicin 600 mg once a month (supervised)

Treatment of paucibacillary leprosy (PB)
- Dapsone 100 mg daily
- Rifampicin 600 mg once a month (supervised)
- The duration of treatment is 6 months, and the patient should be followed up for 5 years

Dapsone Resistance
- This is treated either by clofazimine alone or by combination treatment with ethionamide 500 mg daily and rifampicin given on the first 2 days of each month.

Treatment of Reactional States
- During reactional states, the chemotherapy for leprosy is maintained in addition to the anti-inflammatory drugs given below:
- *Type 1 lepra reaction* (*reversal reaction*). Mild cases are treated with aspirin 600 mg 6 hourly. Severe cases are treated with prednisone 40–80 mg daily, reducing gradually over 3–9 months.
- *Type 2 lepra reaction* (*erythema nodosum leprosum*). Mild cases are treated with aspirin 600 mg 6 hourly. Severe cases are treated with prednisone (1 mg/kg/day). In patients not responding to steroids, clofazimine (300 mg/day) or thalidomide (100 mg 4 times daily) should be added to prednisone. The doses are reduced slowly over 1–3 months. Eye involvement is treated with 1% hydrocortisone drops or ointment and 1% atropine drops.

National Programme
- The National Leprosy Control Programme was launched by the Government of India in 1955 based on Dapsone monotherapy.
- Multidrug Therapy (MDT) came into wide use from 1982 and the Programme was redesignated as the National Leprosy Eradication Programme (NLEP) in 1983.
- The Programme was expanded with World Bank assistance and the first phase of World Bank supported National Leprosy Elimination Project started from 1993–94 and ended in March 2000. The second phase of World Bank supported National Leprosy Elimination Project started from 1 April 2001 for a period of 3 years with the objective to achieve elimination of leprosy as a public health problem by 2005, thereby reducing the case load to less than 1 per 10,000 population. During the second National Leprosy Elimination Project, the NLEP was decentralised to States/Districts and Leprosy Services were integrated with General Health Care System. Free MDT is now available at all subcentres, PHCs and Government Hospitals and Dispensaries on all working days.
- The NLEP is being continued with Govt. of India funds from January 2005 onwards. Additional support for the programme is continued to be received from the WHO and ILEP (an international federation of 15 non-governmental antileprosy organisations).

Q. Explain in brief about leptospirosis.

Q. Write a short note on Weil's syndrome.

Aetiology
- Leptospira consists of two species: *Leptospira interrogans*, which is pathogenic and *Leptospira biflexa*, which is saprophytic. The term leptospirosis describes an infection with any of the subtypes or subgroups of *Leptospira interrogans*.
- The organism is a tightly coiled spirochaete with one axial filament.

Epidemiology

- Leptospirosis is the most widespread zoonosis in the world.
- Reservoirs of infection include rodents, skunks, foxes, domestic livestock and dogs. Many animals exhibit a prolonged urinary shedding of the organism.
- Human infection can occur either by direct contact with urine or tissue of an infected animal or indirectly through contaminated water, soil or vegetation. Transmission may occur through cuts, mucous membranes (nasopharynx, conjunctiva, vagina) and possibly unabraded skin.
- The mechanism by which leptospirae cause tissue damage is not very clear. Early in the disease, tissue damage results from a direct toxic damage due to leptospirae. Later in the illness, damage is the consequence of immune response to leptospiral antigens. Damage to blood vessels is common that leads to vasculitis.

Clinical Features

- Most natural infections appear 7–14 days after the exposure.
- Commonly encountered clinical manifestations are fever, headache, myalgia, conjunctival suffusion, gastrointestinal symptoms like nausea, vomiting and abdominal pain, cough, pharyngitis, lymphadenopathy, hepatomegaly and skin rashes.
  - The fever is usually high-grade with chills and rigors.
  - Headache is severe and is retro-orbital or occipital.
  - Severe myalgias occur in most patients, the muscles of the thighs and lumbar areas being most prominently involved. Myalgia is accompanied by severe muscle tenderness and cutaneous hyperaesthesia (causalgia).
  - Conjunctival suffusion is very helpful in detecting the disease. It is not conjunctivitis, but rather a pericorneal reddening or hyperaemia.
- Less commonly encountered manifestations are splenomegaly, uveitis and diarrhoea.
- The features last for 4–9 days.
- In many cases, the first phase (leptospiraemic phase) is followed by a period of apparent recovery, after which the symptoms worsen again for another 2–5 days (immune phase). During the second phase, meningitis and iridocyclitis are more common.
  - The initial "first phase" or "leptospiraemic phase" is so named because leptospirae are present in the blood and CSF during this phase.
  - The subsequent "second phase" or "immune phase" is so named because of the presence of leptospiral antibodies in the blood, the disappearance of leptospirae from the blood and the onset of urine cultures positive for the organism.
- Presence of headache, fever, neck stiffness or pain due to myalgias may suggest meningitis. The CSF is usually acellular in the first 7 days of illness, although the organisms may be seen. With the onset of antibodies in the serum aseptic meningitis occurs in 90% of patients, with an abnormal CSF (see investigations).
- Other less often seen manifestations are change in the level of consciousness, encephalitis, cranial nerve palsies and acute dilatation of the gall bladder with cholecystitis.

Weil's Syndrome

- Weil's syndrome is not a specific subgroup of leptospirosis; it is simply severe leptospirosis.
- Can develop as the second phase of a biphasic illness or as a progressive illness.
- The overall picture in Weil's syndrome is striking and is characterised by intense jaundice, mental status changes, haemorrhage, purpura or petechiae and renal insufficiency.
  - The first manifestation of severe disease is usually jaundice that develops between 5th and 9th days. Jaundice does not seem to be due to hepatocellular damage, but seems to be more related to the cholestasis of sepsis.
  - Renal insufficiency may develop concomitantly or later, with progressive oliguria and renal failure from acute tubular necrosis.
  - Haemorrhagic manifestations are common and include purpura and petechiae appearing on oral, vaginal or conjunctival mucosa. Other haemorrhagic manifestations include epistaxis, haemoptysis, gastrointestinal bleeding, haemorrhage into adrenal glands and subarachnoid haemorrhage.

Investigations

- Urinary findings early in the illness include microscopic haematuria, pyuria and proteinuria.
- Total leucocyte count may vary, but neutrophilia of more than 70% is very frequent.
- Anaemia may occur due to intravascular haemolysis, azotaemia and blood loss from haemorrhage.
- Hyponatraemia is common.
- Thrombocytopenia and raised erythrocyte sedimentation rate (ESR).

- Liver function tests reveal an elevation of AST and ALT up to five times normal, conjugated hyperbilirubinaemia and raised alkaline phosphatase. Marked elevations of bilirubin with mildly elevated transaminases are characteristic features of Weil's syndrome.
- Elevation of blood urea nitrogen (BUN) and hyperkalaemia occur with renal failure.
- Coagulation studies may show a prolongation of prothrombin time that is reversible with vitamin K.
- Levels of creatine phosphokinase (CPK) are elevated in 50% of patients in the first weak of illness. This is helpful in differentiating the disease from viral hepatitis.
- Chest radiograph may show patchy bronchopneumonia and a small pleural effusion.
- Electrocardiographic abnormalities include bradycardia, low voltage and non-specific ST–T wave changes.
- CSF may be abnormal in up to 90% of cases after 7 days of illness. The cell counts are raised (but <500/mm^3) with a neutrophil predominance. Proteins may be normal or elevated while glucose remains normal. In presence of severe jaundice, xanthochromia can develop.
- The tightly coiled spirochaete in the urine may be visualised by phase contrast or dark-field microscopy.
- IgM antibodies may be detected in blood in the second phase of illness using microscopic agglutination test (MAT).
- Demonstration of leptospira antigen by radioimmunoassay or ELISA.
- The diagnosis can be confirmed by culture (on Fletcher's medium) of the blood in the 1st week of illness or of the urine thereafter. However, this is a tedious process.
- Newer methods include detection of bacterial DNA in various clinical samples.

Treatment

- A variety of antimicrobial agents have been found to be effective in vitro, but the recommended drugs are given below:
    - Intravenous penicillin (1.5 million units 6 hourly) or ampicillin (1 g 6 hourly) for 7 days is beneficial, even when the treatment is started after the 5th day of illness.
    - Doxycycline (100 mg orally twice daily) or ampicillin (750 mg four times daily) for 7 days or azithromycin (500 mg once a day), when started within 4 days of onset of symptoms, is also effective in mild cases.
    - Ceftriaxone (1 g twice a day) has also been shown to be effective.
- Renal failure and jaundice require meticulous attention of fluid and electrolyte therapy. Renal failure may require dialysis. Exchange transfusion may be beneficial in severe hyperbilirubinaemia.
- Anaemia and thrombocytopenia may require blood transfusion.

Q. What is candidiasis (moniliasis)?

- Infection of skin or mucous membranes (e.g. oral cavity and vagina) is called moniliasis.
- *Candida albicans* is the most common cause of candidiasis.
- Invasive candidiasis can also be due to non-*albicans Candida* species (e.g. *C. glabrata*). Some of these are resistant to fluconazole.
- It causes the following conditions of medical importance:
    - Oral thrush. Conditions that favour oral *Candida* infection include use of broad-spectrum antibiotics, xerostomia, immune dysfunction (e.g. diabetes, immunosuppressive therapy, HIV infection, etc.) or presence of removable prostheses. Furthermore, about one in four patients with lichen planus will have superimposed candidiasis.
    - Vaginal candidiasis occurs more commonly in diabetics.
    - Cutaneous candidiasis presenting as intertriginous infection, paronychia, balanitis, pruritus ani, vulval candidiasis (in diabetic females) and scrotal candidiasis.
    - Chronic mucocutaneous candidiasis in immunocompromised patients with leukaemias, lymphomas and AIDS.
    - Oesophageal candidiasis presenting as dysphagia and retrosternal pain.
    - Candidiasis of the urinary tract presenting with haematogenous renal abscess and bladder thrush.
    - Haematogenous dissemination of *Candida* (invasive candidiasis or candidaemia) presenting with retinal abscesses extending into vitreous humor, pulmonary candidiasis, endocarditis, chronic meningitis and arthritis.

Treatment

- Topical application of antifungal agents like nystatin, clotrimazole or miconazole
- Swallowing nystatin suspension or sucking on clotrimazole troches for oesophageal candidiasis
- Systemic antifungal agents: ketoconazole (200–400 mg/day), fluconazole (200 mg/day) or itraconazole 100 mg (200 mg in oesophageal candidiasis) per day for 2 weeks. For oesophageal candidiasis, therapy extended for 3 weeks or 2 weeks after the symptoms subside, whichever is longer.
- Severe systemic infections may require intravenous fluconazole (6 mg/kg/day) or amphotericin B. Echinocandins are newer class of antifungals that include caspofungin, micafungin and anidulafungin. These agents have limited

toxicity, are safe in presence of renal or hepatic impairment, have minimal drug interactions and importantly, have broad-spectrum activity against most *Candida* spp.

Q. Discuss briefly about β-lactamases.

Q. Write a short note on New Delhi metallo-β-lactamase (NDM-1).

β-lactamases

- Production of β-lactamases is the most important contributing factor to β-lactam antibiotic resistance in Gram-negative bacteria.
- β-lactamases are bacterial enzymes that inactivate β-lactam antibacterials by hydrolysis, which results in ineffective compounds. They are not effective against higher generation cephalosporins, e.g. cefotaxime, ceftazidime, ceftriaxone, or cefepime.
- Several serine active β-lactamases inhibitors (clavulanic acid, sulbactam and tazobactam) in combination with β-lactams have been in use to reduce resistance due to presence of β-lactamases.

Extended-Spectrum β-Lactamases (ESBL)

- Several isolates of *Enterobacteriaceae* and *Pseudomonas* produce newer β-lactamases. These enzymes include plasmid-mediated cephamycinases, extended-spectrum β-lactamases (ESBLs), and carbapenem-hydrolysing enzymes or carbapenemases.
- The ESBLs are a group of enzymes that have the ability to hydrolyse and cause resistance to the oxyimino-cephalosporins (cefotaxime, ceftazidime, ceftriaxone, cefuroxime and cefepime) and monobactams (aztreonam), but not the cephamycins (cefoxitin, cefotetan) or carbapenems (imipenem, meropenem, doripenem and ertapenem).
- These enzymes are also inhibited by classical β-lactamase inhibitors such as clavulanic acid, sulbactam and tazobactam.
- ESBLs are often located on large plasmids that also harbour genes for resistance to other antimicrobial classes that include resistance to aminoglycosides and cotrimoxazole. This complicates antimicrobial selection especially in patients with serious infections such as bacteraemia.
- Antimicrobials that are regularly used for empirical therapy of serious community-onset infections, such as the third-generation cephalosporins (e.g. cefotaxime and ceftriaxone), are often not effective against ESBL-producing bacteria.
- As a result of these major concerns, the carbapenems, including imipenem, meropenem, doripenem and ertapenem, have become widely recognised as the drug class of first choice for the treatment of serious infections due to ESBL-producing bacteria. Piperacillin/tazobactam is also useful for the treatment of some infections with ESBL-producing pathogens. Tigecycline has shown excellent activity against ESBL-producing *E. coli* isolates.

New Delhi Metallo-β-Lactamase (NDM-1)

- A novel metallo-β-lactamase (MBL) coded by a novel gene *bla* (NDM-1) in *Enterobacteriaceae*. It is a carbapenemase beta lactamase enzyme.
- It was first reported in a Swedish patient, a diabetic male, who returned to Sweden after having received treatment at a hospital in New Delhi for gluteal abscess in December 2009. Since the immediate previous treatment was traced to New Delhi, it was named as NDM-1.
- Subsequently, organisms in the *Enterobacteriaceae* family containing this genetic element have been found widely throughout India, Pakistan and Bangladesh, and also in Britain and many other countries.
- MBLs are enzymes that mediate resistance to almost all β-lactam agents (except monobactams, e.g. aztreonam) including carbapenems.
- Srains carrying this gene demonstrate multidrug resistance being susceptible only to tigecycline and colistin.

Q. Explain briefly about community-acquired methicillin-resistant *Staphylococcal aureus* (CA-MRSA).

- First recognised in the mid-1990s.
- Refers to strains of MRSA seen in patients presenting with infections in the community or presenting to the hospitals for the first time.
- Typical patients include previously healthy people, often younger, those involved in close contact activities, e.g. sports teams or military service, especially those resulting in skin abrasions.
- Tend to produce more aggressive skin and soft tissue infections, necrotising pneumonia, septic shock and bacteraemia.
- In mild cases, oral treatment with clindamycin, doxycycline, cotrimoxazole or linezolid is useful. Fluoroquinolones should not be used to treat skin and soft tissue infections due to MRSA.
- In severe cases, intravenous vancomycin, teicoplanin, linezolid, tigecycline and daptomycin are also beneficial.

Q. Discuss briefly the life cycle of malarial parasite.

Q Briefly outline stable malaria and unstable malaria.

Q. Discuss the aetiology, epidemiology, clinical features, complications, investigations and management of malaria.

- Malaria is a protozoan disease transmitted by the bite of *Anopheles* mosquitoes.
- Four species of the genus *Plasmodium* infect humans. These are *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*. A comparison of the developmental characteristics of these species is given in the box.
- *P. falciparum* causes the most severe forms of the disease. *P. vivax* infection is the most common in India.

Features	P. falciparum	P. vivax	P. ovale	P. malariae
• Erythrocytic cycle	48 hours	48 hours	48 hours	72 hours
• Red cells parasitised	All	Reticulocytes	Reticulocytes	Mature erythrocytes
• Relapse	No	Yes	Yes	No
• Drug resistance	Yes	No	No	No

Life Cycle of Parasite

- Human infection begins when a female anopheles mosquito inoculates the sporozoites from its salivary gland during a blood meal. They are rapidly carried via the bloodstream to the liver where they enter the hepatocytes.
- In the hepatocyte, during phase of asexual reproduction (intrahepatic or pre-erythrocytic schizogony), a single sporozoite produces thousands of merozoites. The swollen hepatocyte bursts and discharging these merozoites into the bloodstream.

- In *P. vivax* and *P. ovale* infections a proportion of the intrahepatic forms enter a cryptobiotic phase in which they are termed hypnozoites. They may lie dormant for months before starting to divide. These sleeping forms are the cause of the relapses that characterise infection with these two species
- In *P. falciparum* and *P. malariae* infections there is no cryptobiotic phase and therefore relapses from the liver do not occur

- After the entry into the bloodstream, these merozoites rapidly invade erythrocytes. Inside the erythrocyte, asexual division occurs and the parasites develop through "ring" forms to trophozoites and finally to schizonts containing daughter merozoites. The duration of this erythrocytic cycle is 48 hours for falciparum, vivax and ovale, but 72 hours for malariae. These daughter merozoites are released into the bloodstream by erythrocyte rupture. Each of these daughter merozoites is capable of invading a new erythrocyte and repeating the cycle.
- A minor proportion of the merozoites within erythrocytes can undergo a different pathway of development into male and female gametocytes. The gametocytes are ingested by the mosquito during a blood meal. The male and female gametocytes fuse in the insect's midgut to form a zygote. This matures to form an ookinete, which penetrates the gut wall and form an oocyst. The oocyst expands by asexual division giving rise to sporozoites that migrate to the insect's salivary gland. During the blood meal, these sporozoites are inoculated into the next human, thus completing the life cycle.

Epidemiology

- Malaria occurs throughout most of the tropical regions of the world.
- Malaria endemicity is traditionally defined in terms of spleen rates in children—i.e. percentage of children with a palpable spleen.

Term	Spleen rate in children
• Hypoendemic	<10%
• Mesoendemic	11–50%
• Hyperendemic	51–75%
• Holoendemic	>75%

- Stable malaria: In holoendemic and hyperendemic areas where there is intense malaria transmission, the people are infected repeatedly throughout their lives, starting from childhood. By the time of adulthood the immunity is high and malaria infections are largely asymptomatic. This is termed "stable malaria". The predominant organism in these areas is *P. falciparum*.

- Unstable malaria: In hypoendemic and mesoendemic areas where malaria transmission is low, the immunity is low and symptomatic disease occurs at all ages. This is termed "unstable malaria". The predominant organism is *P. vivax*.
- *P. falciparum* does not grow well in red cells that contain haemoglobin F, C or especially, haemoglobin S heterozygotes (AS) are protected against the lethal complications of malaria.
- Attachment of merozoites to red cells is mediated via a specific receptor on the surface of cells. In the case of *P. vivax*, this receptor is related to the Duffy blood group antigen (Fy^a or Fy^b). If a person is Duffy-negative (as most of the West African population is), he will be resistant to infection by *P. vivax*.
- Chloroquine resistance is quite common in north-east part of India. Many strains of P. falciparum are resistant to chloroquine as well as combination of Sulfadoxine and pyrimethamine (multiple drug resistance).

MOSQUITO

Oocyst ← Ookinete ← Zygote

Invasion of gut wall

Asexual division → ... Gametes

Sporozoites → Gametocytes

HUMAN

Blood meal .... Blood meal

Invasion of hepatocytes

Sporozoites → Invasion of erythrocyte ← Gametocytes

Dormancy (hypnozoites)

Asexual division

Merozoites ... Merozoites ← Schizont

Trophozoite **ASEXUAL DIVISION**

Invasion of erythrocyte ← Ring form

HEPATOCYTE .... **ERYTHROCYTE**

Merozoites

Invasion of erythrocyte

BLOODSTREAM

Clinical Features

Vivax, Ovale and Malariae Malarias

- Incubation period for *P. vivax* is 12–17 days, for *P. ovale* it is 15–18 days, and for *P. malariae* it is 18–40 days.
- Prodromal symptoms are more severe with *P. malariae* infections.
- These "benign" malarias also present with paroxysmal feverish symptoms. In vivax and ovale malaria infections, the characteristic tertian interval (48 hours interval between fever spikes or fever on alternate days) may be seen. In *P. malariae* infections, the quartan interval (72 hours interval between spikes or fever every 3rd day) may be seen.
- Patients suffering from vivax malaria may become anaemic, thrombocytopenic and mildly jaundiced with tender hepatosplenomegaly. Splenic rupture is more common with vivax malaria.
- The acute symptoms of ovale and malariae malarias may be as severe as those of vivax infection, but anaemia is less severe and the risk of splenic rupture is lower.
- *P. malariae* infections are associated with gross splenomegaly, but splenic rupture is less common. *P. malariae* causes glomerulonephritis and an immune complex nephropathy resulting in nephrotic syndrome.
- Vivax and ovale malarias have a persistent hepatic cycle that may give rise to relapses. *P. malariae* does not relapse, but a persisting undetectable parasitaemia may cause repeated exacerbations.
- Occasionally, vivax malaria can produce complications similar to those of falciparum malaria. This has been increasingly reported from India.

Falciparum Malaria (Malignant Tertian or Subtertian Malaria)

- The incubation period ranges from 7 to 14 days (mean 12 days).
- Prodromal symptoms like malaise, headache, myalgia, anorexia and mild fever may last for several days before the onset of the classical "malarial paroxysms".
- In a classical malarial paroxysm, suddenly the patient feels inexplicably cold and apprehensive. Mild shivering follows, which quickly turns into violent shaking with teeth rattling. There is intense peripheral vasoconstriction and goose flesh. The rapid increase in temperature may trigger febrile convulsions. The rigor lasts up to 1 hour. This is followed by a hot flush with throbbing headache, palpitations, tachypnoea, prostration, postural syncope and vomiting. The temperature reaches its peak. Finally, a drenching sweat breaks off and the fever defervesces over the next few hours. The exhausted patient sleeps off. The whole paroxysm lasts about 8–12 hours.
- A high irregularly spiking unremitting fever or daily (quotidian) paroxysm is more commonly seen in falciparum malaria than the classically described tertian or subtertian periodicity (48 and 36 hours between fever spikes).
- The patient with falciparum malaria usually looks severely ill with "typhoid" facies.
- The patient is often anaemic and jaundiced with moderate tender enlargement of the spleen and liver.
- Neurological complications of falciparum malaria can manifest as acute headache, irritability, agitation, seizures, psychosis and impaired consciousness.

Jaundice in Malaria

- Occurs due to severe haemolysis and hepatic involvement (malarial hepatopathy).
- The parasite, especially *P. falciparum* infects a large number of cells that are then destroyed in the spleen, resulting in haemolytic anaemia. This is characterised by elevated serum bilirubin (dominant unconjugated fraction), without any significant elevation of the liver enzymes.
- "Malarial hepatitis" or malarial hepatopathy:
  - This term is commonly used to describe hepatocytic dysfunction in severe and complicated malaria; however, actual inflammation of the liver parenchyma is almost never seen.
  - Occurs due to sequestration of the parasite-infested red blood cells in the capillaries (due to adherence to endothelial cells as well as rosette formation) causes clogging of the capillaries in the hepatic microvasculature.
  - Characterised by a rise in serum conjugated bilirubin along with the rise in serum glutamate pyruvate transaminase levels to more than three times the upper limit of normal. This elevation occurs in the absence of evidence of exposure to hepatotoxic drugs and absence of clinical or serological evidence of viral hepatitis.
  - Prothrombin time is usually normal.
- Some cases have superimposed hepatitis viral infections (e.g. Hepatitis E) to produce jaundice and hepatic function derangement.
- DIC can also contribute to liver dysfunction and haemolysis.

Severe Manifestations and Complications of Falciparum Malaria

- WHO defines complicated falciparum malaria as one of the features shown in the box along with presence of asexual forms of *P. falciparum* in the peripheral smear. Acute renal failure, acute respiratory distress syndrome and jaundice are uncommon in children.

- Highest risk of complications from malaria are found in non-immune people, children and pregnant females who live in endemic regions.

Criteria for Severe and Complicated Malaria

Complication	Definition
• Cerebral malaria	Impaired consciousness, unrousable coma
• Repeated generalised convulsions	Two convulsions within 24 hours
• Severe anaemia	Haemoglobin concentration <5 g/dL
• Renal failure	Serum creatinine >3 mg/dL, oliguria
• Respiratory distress	Acidotic breathing, pulmonary oedema, acute respiratory distress syndrome
• Hypoglycaemia	Blood glucose <40 mg/dL
• Circulatory collapse or shock	Systolic BP <90 mmHg, rapid thready pulse
• DIC	Bleeding from different sites of the body
• Acidosis	pH <7.25
• Blackwater fever	Macroscopic haemoglobinuria (cola coloured urine)
• Jaundice	Bilirubin >3 mg/dL
• Hyperparasitaemia	>5% of erythrocytes infested by parasites

Cerebral Malaria

- Cerebral malaria is defined as diffuse encephalopathy not attributable to any other cause in a patient with falciparum malaria.
- Convulsions occur in both children and adults, but are more common in children.
- Retinal haemorrhages may occur and is associated with a poor prognosis. Papilloedema is rare.
- A variety of transient abnormalities of eye movement, especially dysconjugate gaze, have been noted.
- Fixed jaw closure and tooth grinding (bruxism) are common.
- Pouting may occur or a pout reflex may be elicited by stroking the sides of the mouth.
- The most common neurological signs in adults are those of a symmetrical upper motor neuron lesion. The abdominal reflexes are invariably absent.
- Motor abnormalities like decerebrate rigidity, decorticate rigidity and opisthotonus occur.
- Neuropsychiatric manifestations, cerebellar signs, extrapyramidal syndromes and multiple cranial nerve involvement are common in Indian patients.
- Residual neurological sequelae occur in about 5% of adults and 10% of children. These include hemiplegia, cortical blindness, aphasia and ataxia and occur more frequently in patients with prolonged coma, protracted convulsions, severe anaemia and biphasic clinical course.
- Bad prognostic signs include prolonged impaired consciousness, respiratory failure, renal failure, jaundice and hypoglycaemia.
- The CSF pressure is usually normal. The fluid is clear with less than 10 cells per μL, CSF lactic acid and protein levels are elevated.

Anaemia

- Anaemia is common in severe malaria. It is often associated with secondary bacterial infection, retinal haemorrhages and pregnancy.
- The causes of anaemia in malaria are:
  - Haemolysis of infected and uninfected erythrocytes.
  - Dyserythropoiesis.
  - Splenomegaly causing erythrocyte sequestration and haemodilution.
  - Depletion of folate stores.

Renal Failure

- Renal failure usually occurs in adults. There is a progressive oliguria eventually leading to anuria. Renal failure results from acute tubular necrosis. The serum creatinine and urea levels progressively increase.
- The acute renal failure associated with malaria is usually reversible.

Hypoglycaemia

- Hypoglycaemia is a frequent complication of falciparum malaria. It occurs in three different groups of patients:
  - Patients with severe disease, especially young children.

- Patients treated with quinine or quinidine.
- Pregnant females, either on admission or following quinine treatment.
- In malaria, hypoglycaemia can occur due to various mechanisms:
  - Failure of hepatic gluconeogenesis.
  - Increased consumption of glucose by host and parasite.
  - Treatment with quinine or quinidine results in stimulation of pancreas to secrete insulin. The resulting hyperinsulinaemia causes hypoglycaemia.

Fluid, Electrolyte and Acid–Base Disturbances

- Hypovolaemia manifests as low jugular venous pressure, postural hypotension, oliguria and high urine specific gravity. This may be accompanied by signs of dehydration.
- Acidotic breathing may be seen in severely ill patients in shock, hypoglycaemia, hyperparasitaemia and renal failure.
- Lactic acidosis is a common complication and both blood and CSF lactic acid levels are elevated.

Pulmonary Oedema

- This is a grave complication of severe malaria and it carries a high mortality.
- It may appear several days after chemotherapy has been started and at a time when the patient's general condition is improving.
- Pulmonary oedema is associated with hyperparasitaemia, renal failure, pregnancy, hypoglycaemia and lactic acidosis.

Circulatory Collapse ("Algid Malaria")

- Some patients present in a state of collapse, with a systolic blood pressure less than 80 mmHg in the supine position. They have cold, clammy and cyanotic skin, constricted peripheral veins and a rapid feeble pulse.
- This clinical picture is often associated with a complicating Gram-negative septicaemia. Possible sites of infection should be sought—e.g. lung, urinary tract, meninges, IV puncture sites and IV lines.
- Circulatory collapse is also seen in patients with pulmonary oedema, metabolic acidosis, massive gastrointestinal haemorrhage, dehydration and hypovolaemia.

Spontaneous Bleeding and Disseminated Intravascular Coagulation

- Disseminated intravascular coagulation (DIC) complicated by clinically significant bleeding occur commonly in non-immune patients in hypoendemic and mesoendemic areas. Clinical manifestations include haematemesis or melaena, bleeding gums, epistaxis, petechiae and subconjunctival haemorrhages.
- Thrombocytopenia is common (but is unrelated to DIC); however, it is usually not associated with bleeding. The platelet count usually returns to normal after successful treatment of the malaria.

Hyperpyrexia

- This is more common in children and is associated with convulsions, delirium and coma.
- Hyperpyrexia (body temperature >42°C) may cause permanent severe neurological sequelae.

Hyperparasitaemia

- Hyperparasitaemia is associated with severe disease. This is more common in non-immune patients with high parasite densities (>5%).
- In highly endemic areas, patients can tolerate high parasite densities (20–30%) often without clinical symptoms.

Malarial Haemoglobinuria

- Malaria haemoglobinuria is uncommon and is usually associated with hyperparasitaemia and/or severe disease. It may or may not be accompanied by renal failure.
- Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency and some other erythrocyte enzyme deficiencies may develop vascular haemolysis and haemoglobinuria when treated with oxidant drugs such as primaquine.
- Blackwater fever typically occurs in non-immune patients with chronic falciparum malaria, taking antimalarials (especially quinine) irregularly. It occurs more commonly in patients with G6PD deficiency. Blackwater fever is accompanied by mild or absent fever, scanty or absent parasitaemia and dark or black urine. The condition carries a poor prognosis, but is very rare now.

Investigations

Microscopy

- Diagnosis of malaria rests on the demonstration of asexual forms of the parasites in peripheral blood smears stained with one of the Romanowsky stains (Wright's, Field's, Leishman's or Giemsa). Both thin and thick smears should be examined. Parasites should be counted in relation to the total white cell count (on thick films when the parasitaemia is relatively low) or erythrocytes (on thin films).
- Sometimes no parasites can be found in peripheral blood smears from patients with malaria even in severe infections. This is explained by partial antimalarial treatment or by sequestration of parasitised cells in deep vascular beds. In these cases, examination of smears of bone marrow aspirate reveals parasites or malaria pigment.
- An alternative and probably more sensitive test than the peripheral smear is the quantitative buffy coat analysis (QBC). In this test, the centrifuged buffy coat is stained with a fluorochrome (e.g. acridine orange) that "lights up" malarial parasites when viewed under UV light.

Immunodiagnosis

- Malarial antibodies can be deleted by serological techniques like immunofluorescent assay (IFA) or enzyme-linked immunosorbent assay (ELISA); however, these tests are not specific and are not done routinely.

Other Laboratory Findings

- A number of simple, sensitive and specific antibody-based diagnostic stick tests have been developed for identifying parasitic enzymes and proteins. Examples include detection of *P. falciparum* specific histidine-rich protein-2 (HRP-2) and plasmodium lactate dehydrogenase antigens (common to all plasmodium species) in finger prick blood samples. HRP-2 can remain positive up to 2–4 weeks after the parasites disappear from blood. Monitoring parasite clearance and parasitic load are not possible with these immunological methods. There is also some cross-reactivity with rheumatoid factor.
- PCR testing for parasite messenger RNA or DNA.
- Normochromic normocytic anaemia, thrombocytopenia and raised ESR.
- Total leucocyte count is low to normal, but neutrophil leucocytosis may be seen in severe infections.
- Plasma viscosity and C-reactive protein levels are high.
- Prothrombin time and partial thromboplastin time may be prolonged in severe infections. Antithrombin III levels are reduced.
- In complicated malaria there may be metabolic acidosis and low plasma concentrations of glucose, sodium, bicarbonate, calcium, magnesium and albumin. Lactate, BUN, creatinine, muscle and liver enzymes, bilirubin and gamma globulin levels may be elevated.
- Neuroimaging in patients with cerebral malaria may demonstrate brain swelling, cortical infarcts and hyperintense areas in white matter.

Management

Management of Uncomplicated Malaria

P. vivax Malaria

- Most cases of vivax malaria are sensitive to chloroquine. Some may be resistant to Sulfadoxine/pyrimethamine.
- Chloroquine is the drug of choice. It is given at a dose of 600 mg base (four tablets) stat, followed by 600 mg base (four tablets) on second day, followed by 300 mg base (two tablets) on third day. Chloroquine resistant *P. vivax* strains are being reported from India.
- If *P. falciparum* is negative using rapid tests or no tests are available, cases showing signs and symptoms of malaria without any other obvious cause for fever should be considered as "clinical malaria". These should be treated with chloroquine in full therapeutic dose of 25 mg/kg body weight over 3 days.
- Artemisinin-based combination therapies are as effective as chloroquine in *P. vivax*.

P. falciparum Malaria

- Chloroquine resistance in falciparum malaria is common and therefore, WHO recommends combination therapy for *P. falciparum* malaria.
- In India, chloroquine resistance is high in north-eastern states, Andhra Pradesh, Chhattisgarh, Jharkhand, Madhya Pradesh and Orissa.

- Artemisinin derivatives produce faster relief of clinical symptoms and faster clearance of parasites from the blood than other antimalarial drugs. When used as monotherapy, short half-life of artemisinin derivatives means that patients must take the drug for at least 7 days. Failure to complete the course, due to rapid improvement in clinical symptoms, can lead to high levels of treatment failure or development of resistance. Therefore, artemisinin derivatives are given with another longer-acting drug. This is known as artemisinin-based combination therapy or ACT. These combinations can then be taken for shorter durations than artemisinin alone.
- These combinations include artemether + lumefantrine, artesunate + amodiaquine, artesunate + mefloquine, dihydro-artemisinin + piperaquine and artesunate + sulfadoxine–pyrimethamine.
- The ACT used in the national programme in India is artesunate + sulfadoxine/pyrimethamine. It is given as:
  - 200 mg artesunate along with sulfadoxine 1500 mg and pyrimethamine 75 mg on day 1.
  - 200 mg artesunate on days 2 and 3.
- For north-east region, resistance to partner drug Sulfadoxine–pyrimethamine have been reported. The national programme advises use of artemether + lumefantrine.
- Another option is to use quinine 600 mg salt three times daily for 5 days orally, followed by a single-dose of Sulfadoxine 1.5 g combined with pyrimethamine 75 mg.
- ACTs can be given in second and third trimester of pregnancy. Recommended treatment in first trimester of pregnancy is quinine.
- If sulphonamide sensitivity is suspected, quinine may be followed by tetracycline 250 mg 6 hourly for 7 days.
- Other drugs for treating chloroquine resistant *P. falciparum* are mefloquine (15 mg/kg followed by 10 mg/kg after 8 hours; generally given as ACT) and halofantrine.
- A new drug launched by India is arterolane maleate (150 mg) plus piperaquine phosphate (750 mg) which is effective against *P. falciparum*. Dose is 1 tablet once a day for 3 days.

Management of Complicated Falciparum Malaria

- Maintenance of airway, anticonvulsant therapy and nursing care.
- Control high fever, hypoglycaemia, seizures and anaemia.

Specific Drug Therapy

- Chloroquine
  - With chloroquine resistance being reported from most parts of India, quinine or artemisinin derivatives are the first-line drug for cerebral malaria. Both are rapidly acting drugs and are combined with slower-acting drugs for complete cure.
- Quinine
  - Quinine is administered (as dihydrochloride salt) in a dose of 20 mg/kg in 5% dextrose over 4 hours followed by 10 mg/kg infusion (over 4 hours) every 8 hours starting 8 hours after beginning of initial dose.
  - It is the drug of choice in first trimester of pregnancy.
  - Important adverse and toxic effects include hypoglycaemia, hypotension, nausea, vomiting and blindness. Therefore, blood glucose should be monitored.
  - A loading dose of quinine should not be used if the patient has received quinine, quinidine or mefloquine within the preceding 12 hours.
  - Once patient becomes conscious, quinine is given orally in a dose of 10 mg/kg three times a day to complete a course of 7 days. Doxycycline 3 mg/kg/day is also started for 7 days. In pregnant women and children, clindamycin 10 mg/kg 12 hourly for 7 days should be used instead of doxycycline.
  - There has been decline in response rate over years to quinine. Also, fever clearance takes more time than artemisinin derivatives. In addition, high frequency of adverse effects is seen. Hence, quinine is not preferred by many physicians as first-line agent.
- Artemisinin derivatives
  - Derivatives of Chinese drug, qinghaosu.
  - Artesunate, artemether, arteether.
  - Clear the parasitaemia rapidly and can be used as first line or after failure of quinine.
  - Artesunate: Three doses of 2.4 mg/kg (120 mg in adults) intravenously at 0, 12 and 24 hours and then 2.4 mg/kg once a day for 6 days.
  - Dose of artemether is 3.2 mg/kg (160 mg in adults) IM followed by 1.6 mg/kg daily for 6 days.
  - Dose of arteether is 150 mg daily IM for 3 days in adults only.
  - Patients receiving artemisinin derivatives should get full course of oral ACT. However, ACT containing mefloquine should be avoided in cerebral malaria due to neuropsychiatric complications.
- Other drugs
  - Use of steroids and mannitol is not recommended.

Radical Cure of Malaria Due to P. Vivax and P. Ovale

- Primaquine is given at a dose of 15 mg daily for 14 days. It destroys the hypnozoite phase in the liver.
- Primaquine may cause haemolysis in patients with G6PD deficiency and cyanosis due to the formation of methaemoglobin in red cells.

Prevention of Transmission of *P. falciparum*

- None of the drugs used to kill *P. falciparum* is gametocidal and hence, the patient acts as a reservoir for transmission of parasite to mosquito.
- To prevent this, the patient should receive primaquine in a single-dose of 45 mg.

Chemoprophylaxis of Malaria

- For short-term chemoprophylaxis (less than 6 weeks), doxycycline in a dose of 100 mg daily. It should be started 2 days before travel and continued for 4 weeks after leaving the malarious area.
- For long-term chemoprophylaxis (more than 6 weeks), mefloquine in a dose of 5 mg/kg (up to 250 mg) weekly. It should be administered 2 weeks before, during and 4 weeks after leaving the area.

Q. Describe tropical splenomegaly syndrome (TSS).

- Also known as hyperreactive malarial splenomegaly.
- Aetiology and clinical manifestations of TSS are as follows:
  - Seen in areas hyperendemic for malaria.
  - Exaggerated immune response to repeated attacks of malaria. There is increased production of IgM antibodies to suppressor (CD8 +) T-lymphocytes that leads to increased and uninhibited IgM production by B cells and formation of cryoglobulins. This immunological process stimulates hyperplasia of the reticulo-endothelial system resulting in splenomegaly.
  - Typically, these patients have only low levels of parasites in the blood. Clinical presentation is with massive splenomegaly, hepatomegaly and occasionally low-grade fever.
  - Vulnerability to respiratory and skin infections are increased.
  - Some cases may evolve into a malignant lymphoproliferative disorder, particularly CLL.
- Diagnosis of TSS
  - High levels of antimalarial antibodies in blood. IgM levels are markedly raised (up to 20 times).
  - Light microscopic examination of liver shows sinusoidal lymphocytosis.
  - Immunofluorescence microscopy of liver biopsy shows IgM aggregates phagocytosed by RE cells.
  - Malarial parasites may be rarely present in peripheral blood.
- Treatment of TSS.
  - Prolonged administration of antimalarials is required. This removes the antigenic stimulus provided by repeated malarial infection and allows the immune system to return to normal.
    - Proguanil 100 mg daily lifelong or chloroquine 300 mg base every week
    - Folic acid 5 mg daily
    - Splenectomy has no role.

Q. Discuss about amoebic liver abscess.

- Involvement of liver by *Entamoeba histolytica* produces amoebic liver abscess. The term amoebic hepatitis is not used at present.

Pathogenesis

- The trophozoites of *E. histolytica* are carried as emboli by the radicles of the portal vein from the base of an amoebic ulcer in the large intestine. The capillary system of the liver acts as an efficient filter and holds these parasites. They multiply in large number and cause coagulation necrosis of the liver and abscess formation.
- In majority, the abscess is single and confined to the posterosuperior aspect of the right lobe of the liver. This is because the right lobe receives most of the blood draining the right colon through the "streaming" effect in portal vein flow.

Clinical Manifestations

- Insidious onset of fever, sweats, weight loss, chills and rigors.
- Some patients have an acute onset of fever.
- There may be pain in the right hypochondrium resulting from stretching of the liver capsule.
- Diaphragmatic irritation may give rise to referred pain in the right shoulder.

- Clinical examination may reveal enlargement and tenderness of the liver, upward extension of the liver dullness on percussion, point tenderness in the posterolateral portion of a lower right intercostal space (intercostal tenderness) and bulging of the intercostal spaces.

Complications

- Spontaneous external rupture may result in "granuloma cutis".
- Direct extension into lung may result in amoebic lung abscess.
- Abscess may rupture into a bronchus and the patient expectorates large amounts of the typical "anchovy-sauce" pus.
- Rupture into pleural space may result in massive pleural effusion.
- Left lobe abscess may rupture into pericardium resulting in pericarditis and rarely cardiac tamponade.
- Rupture into peritoneal cavity may result in peritonitis.
- Metastatic brain abscess, splenic abscess and rupture into stomach are rare complications.

Investigations

- Polymorphonuclear leucocytosis is a characteristic feature.
- Liver function tests may be abnormal. The most consistent abnormality is an elevation of alkaline phosphatase.
- The level of SGOT reflects the severity of the disease. Jaundice is uncommon and when present implies a grave prognosis.
- Chest radiograph commonly shows raised dome of the diaphragm on the right side. Other findings include right-sided pleural effusion and right basal pneumonitis.
- Ultrasonic scanning of liver is very useful in establishing the diagnosis and localisation of the abscess. The defect in liver usually persists for several months after the complete recovery of the patient.
- Isotope liver scans and computed tomography can also detect abscess.
- Serologic tests ("amoebic serology") are positive in more than 90% of the patient.
- Aspiration
  - Needle aspiration yields the characteristic "anchovy sauce" or "chocolate" pus, which consists of liquefied necrotic liver tissue. It is usually thick in consistency, yellow or green in colour and characteristically odourless. The pus does not contain polymorphonuclear leucocytes. As the parasites are localised in the cyst wall, they may be demonstrated in the terminal portion of the aspirate or at times, by a needle biopsy of the cyst wall.

Treatment

- Metronidazole 800 mg thrice daily orally for 7–10 days or tinidazole 2 g daily as a single-dose for 5 days is usually effective. Severe cases may require intravenous metronidazole (500 mg 8 hourly).
- Chloroquine may be given at a dose of 300 mg twice daily for 2 days followed by 150 mg twice daily for 19 more days. It is generally given to a patient who does not show adequate response to metronidazole.
- Emetine and dehydroemetine have a direct lethal action on the trophozoites of *E. histolytica*. However, these agents are very toxic and therefore, are rarely used at present. Their toxicity includes cardiac arrhythmias, precordial pain, muscle weakness, vomiting and diarrhoea. Dehydroemetine is less toxic than emetine.
- Therapeutic aspiration of the pus may be required with large abscesses, those threatening to burst and when the response to chemotherapy is not prompt.
- After treatment furamide should be given at a dose of 500 mg thrice daily for 10 days to eliminate intestinal luminal cysts.

Role of Percutaneous Drainage

- This involves placing a large bore catheter into the abscess. Even multiple abscesses can be drained.
- Percutaneous drainage is generally performed after a therapeutic aspiration has failed and is indicated when:
  - Volume of abscess is large and there is risk of spontaneous rupture (especially left lobe abscesses).
  - Actual rupture has occurred (drainage of both abscess and extraneous collection).
  - There is lack of response to medical therapy with clinical signs of persistent sepsis or enlarging abscesses or persistent symptoms.
  - There is an evidence of liver failure.

Q. Write a note on leishmaniasis.

- Leishmaniasis denotes disease caused by any of the number of species of protozoa in the genus *Leishmania*. There are four major clinical syndromes described:
  - Visceral leishmaniasis (kala-azar)—caused by *Leishmania donovani*.

- Cutaneous leishmaniasis of the old world—caused by *L. major* and *L. tropica*; cutaneous leishmaniasis of the new world—caused by *L. mexicana* and *L. amazonensis*.
- Mucocutaneous leishmaniasis (espundia)–caused by *L. braziliensis*.
- Diffuse cutaneous leishmaniasis---caused by *L. mexicana* and *L. aethiopica*.

Q. Give a brief account of kala-azar or visceral leishmaniasis.

Aetiology

- Kala-azar (visceral leishmaniasis) is a generalised visceral infection by the organism *Leishmania donovani*. It affects the monocytes and macrophages of liver, spleen, bone marrow and lymph nodes.
- The flagellated forms (promastigotes) of the organism develop within the female sandflies (*Phlebotomus argentipes*), which convey the disease to humans.
- In humans, the organism is seen in the cells of monocyte–macrophage system as oval bodies known as amastigotes (Leishman–Donovan bodies or LD bodies).

Epidemiology

- Endemic in several countries; of all kala-azar cases, more than 90% are from India, Bangladesh, southern Sudan, Nepal and Brazil.
- Kala-azar is endemic in several parts of India. Most cases occur in the states of Bihar, West Bengal, eastern parts of Uttar Pradesh, Jharkand and parts of Orissa.
- Sporadic cases have been reported from several other parts of India.

Clinical Features

- Some patients present with a low-grade fever, whereas others present with a high-grade, intermittent fever showing a double rise of temperature in 24 hours ("camel hump fever").
- Anaemia, lymphadenopathy (the latter is more common in patients from West Bengal).
- Massive splenomegaly and hepatomegaly.
- Generalised pigmentation, particularly over face is common (kala-azar means "black fever").

Complications

- Complications include repeated infections (including tuberculosis and malaria), malnutrition and cancrum oris.

Investigations

- Anaemia, granulocytopenia and thrombocytopenia.
- Low serum albumin and high serum globulin, especially IgG.
- Mild elevation in bilirubin, AST/ALT and alkaline phosphatase.
- Demonstration of amastigotes (LD bodies) in stained smears of aspirates of bone marrow, liver, spleen, lymph nodes or buffy coat of peripheral blood. Bone marrow is positive in 50–70% cases while splenic aspirate is positive in 70–90% cases.
- Culture of the aspiration in the Novy–MacNeal–Nicolle (NNN) medium for the organism.

Immunodiagnostic Tests

- These are less invasive and are useful in community surveillance studies.
- The skin test to demonstrate delayed-type hypersensitivity (Leishmanin skin test) is positive only in patients with cured kala-azar.
- Increased production of immunoglobulins—Napier's aldehyde test and Chopra's antimony test (non-specific).
- Specific antibody detection by complement fixation test, indirect haemagglutination test, indirect fluorescent antibody test and countercurrent immunoelectrophoresis have poor sensitivity and specificity. Direct agglutination test (DAT) is simple, quick, cheap and specific test that can be applied in the field conditions. Another antibody detection test is based on using recombinant K39 antigen-impregnated nitrocellulose strips that has shown excellent results in field setting. The drawback of these tests is that they remain positive for more than 5 years after complete cure of the patient.
- Antigen detection by reverse western blotting, dot enzyme immunoassay (EIA) and latex agglutination test.
- DNA detection by PCR.

Post-Kala-Azar Dermal Leishmaniasis (PKDL)

- Recovery may be followed by post-kala-azar dermal leishmaniasis.
- It occurs in about 10% cases several months or even years after successful treatment of kala-azar.

- In 15–20% of PKDL cases, no preceding history of kala-azar is available, suggestive of subclinical infection.
- Contributes to spread of infection to sandflies by providing reservoir of infection.
- It presents with hypopigmented macules, papules or nodules. Three types of skin lesions can occur in varying combinations:
  - Erythematous indurated lesions on the butterfly area of face.
  - Multiple symmetrical hypopigmented macules with irregular margins that may coalesce, having generalised distribution to the extremities and trunk.
  - Combination of papules, nodules and plaques.
- Diagnosis is by demonstration of parasite in the slit smear or by culture of the dermal tissue.

Treatment

- Blood transfusions is to correct anaemia and treatment of intercurrent bacterial infections with antibiotics.

Pentavalent Antimonials

- Pentavalent antimonials (sodium stibogluconate, meglumine) have been the mainstay of antileishmanial therapy for the past several decades. The dose is 20 mg/kg for 40 days. However, a large number of patients fail to respond due to parasitic resistance. Important side effects include myalgias, abdominal pain, abnormalities of liver enzymes, T-wave abnormalities; and in rare cases, death from cardiac causes.
- For PKDL prolonged treatment for 3–4 months is required.

Pentamidine

- Pentamidine in a dose of 3–4 mg/kg on alternate days for 5–25 weeks was recommended as a second-line drug in patients who failed to respond to antimony. However, its effectiveness has reduced over the years with cure rates of only 70–80% reported in recent years. Important side effects are hypoglycaemia and induction of diabetes mellitus.

Amphotericin B

- At present, amphotericin B is recommended either as the primary drug of choice or as a second-line drug in patients unresponsive to antimonials. It is almost 100% curative. Dose is 0.75–1.0 mg/kg/day given on alternate days for 15–20 doses. Side effects include fever with chills, hypokalaemia and renal impairment. Some of these side effects can be reduced by using lipid preparations of amphotericin B, but these formulations are very costly. These include liposomal amphotericin B, amphotericin B lipid complex and amphotericin B colloidal dispersion.
- Liposomal amphotericin B at a single-dose of 10 mg/kg has been shown to be as effective as 15 days of conventional amphotericin B. It may be combined with 7–14 days of oral miltefosine.

Miltefosine

- Miltefosine, an oral drug, has shown excellent results and is the first highly effective, orally administered drug for treating visceral leishmaniasis as well as PKDL.
- Dose is 50 mg once a day if weight is less than 25 kg and 50 mg twice a day if weight is more than 25 kg. Duration of treatment is 4 weeks for kala-azar and 12 weeks for PKDL.
- Toxic effects include gastrointestinal symptoms such as vomiting and diarrhoea and occasionally, reversible hepatotoxicity and nephrotoxicity.
- Should not be used in children below 2 years of age, HIV positive patients, pregnant and lactating women and women of reproductive age who refuse to use contraceptives during the treatment period and two months after completion of treatment.

Other Drugs

- Paromomycin (aminosidine) is highly effective and safe drug that needs to be given parenterally.
- Oral imidazoles (ketoconazole, fluconazole) are not very effective in the treatment of kala-azar.
- Interferon-γ in combination with antimonials.

Q. Discuss the aetiology, clinical manifestations, diagnosis and management of toxoplasmosis.

Q. Describe briefly about congenital toxoplasmosis.

- Toxoplasmosis is caused by the protozoan *Toxoplasma gondii*.

Transmission

- Man is the intermediate host while cat is the definitive host.
- Ingestion of oocysts from contaminated soil or bradyzoites from undercooked meat, contaminated vegetables or water.

- Transplacental transmission results in congenital toxoplasmosis.
- Occasionally, blood-borne transmission.

Clinical Manifestations

Infection in Immunocompetent Host

- Most often, acute toxoplasmosis is asymptomatic.
- In symptomatic patients, the most common presentation is cervical lymphadenopathy. Some cases have generalised lymph node enlargement. Other features include fever, malaise and myalgias.
- Uncommon features are skin rash and confusion.
- Myocarditis, encephalitis, pneumonia and polymyositis occur rarely.
- Symptoms resolve within a few weeks.

Ocular Infection

- Most cases of ocular involvement (chorioretinitis) occur after congenital infection.
- Blurred vision, scotomas, photophobia and eye pain.
- Loss of vision.
- Episodic flare-ups can occur.
- Examination shows grey-white foci of retinal necrosis with adjacent choroiditis, vasculitis, haemorrhage and vitreitis.
- Anterior uveitis may also be seen.

Infection in Immunocompromised Host

- The infection in immunosuppressed patients is usually due to reactivation of latent infection.
- Most common involvement is of the central nervous system.
- Encephalopathy, meningoencephalitis, seizures, headache and focal neurological deficits are common.
- Pneumonia and ocular involvement are also common.

Congenital Toxoplasmosis

- Cerebral manifestations like hydrocephalus or microcephaly, convulsions, tremors, paralysis and patches of calcification in the brain are visible on radiograph.
- Cerebrospinal fluid may be xanthochromic with increased protein and mononuclear cells.
- Microphthalmos, nystagmus, chorioretinitis and blindness.
- Hepatomegaly, jaundice, thrombocytopenia and purpura may also occur.

Diagnosis

- Minimal lymphocytosis, elevated ESR and mild increase in liver enzymes
- Antibodies are detectable in the blood. A rise in titre of IgM antibodies indicates acute infection. However, most cases of toxoplasmosis in immunocompromised patients are due to re-activation where there is no rise in IgM antibody. Hence, IgG antibodies are used for presumptive diagnosis.
- PCR for toxoplasma DNA in ocular secretions.
- Biopsy material from a lymph node may be inoculated into mice or may show characteristic histologic changes and any of the three infectious stages: tachyzoites in groups, bradyzoites (tissue cysts) or sporozoites within oocysts.
- Toxoplasma encephalitis:
  - CSF may be normal or shows mild increase in cells and protein.
  - IgG antibodies to toxoplasma.
  - CT scan of head shows multiple contrast-enhancing lesions.
  - MRI is more sensitive than CT scan in picking the lesions.
  - Single-photon emission computed tomography (SPECT) is an important tool for differentiating CNS lymphoma from toxoplasmic encephalitis.

Management

- A combination of sulphadiazine (1 g 6 hourly) and pyrimethamine in a single loading dose of 200 mg followed by 50–75 mg daily, both for 4–6 weeks, along with leucovorin. In patients sensitive to sulphonamides, clindamycin or azithromycin can be used.
- Steroids are added for ocular toxoplasmosis.
- If a seronegative female acquires toxoplasmosis during pregnancy (especially in the first trimester), or seroconverts during pregnancy, there is a high risk of her giving birth to an infant with congenital toxoplasmosis. Termination of pregnancy should be considered in such cases.

Q. Write a short note on taeniasis solium and cysticercosis.

Q. Briefly explain neurocysticercosis.

- *Taenia solium*, the pork tapeworm, inhabits the intestinal lumen of humans, its only a definitive host. Pigs are the usual intermediate hosts. Humans acquire the infection following eating of undercooked pork containing cysticerci.
- When human tissue is invaded by the larval form, the condition is referred to as cysticercosis. Human cysticercosis results from ova being swallowed or gaining access to the human stomach by regurgitation from the person's own adult worm. The larvae are liberated from eggs in the stomach, penetrate the intestinal mucosa, and are carried to many parts of the body where they develop and form cysticerci. The common locations are subcutaneous tissue, skeletal muscles, eyes and brain.

Clinical Features

- Presence of adult worm in the intestine is generally asymptomatic.
- Superficially placed cysts may be palpable under the skin or mucosa as pea-like ovoid bodies.
- The dead larvae may invoke marked tissue response with muscular pain, weakness, fever and eosinophilia.
- Neurocysticercosis results from brain cysts. It may manifest as meningoencephalitis, epilepsy, personality changes, staggering gait, space-occupying lesion, stroke (due to inflammatory changes in the wall of intracranial arteries located in the vicinity of cysticerci) or hydrocephalus.

Diagnosis

- Eggs and proglottids in stool.
- Soft tissue radiographs may show calcified cysts (cigar-shaped) in muscles.
- CT scan of the brain may show calcified spots, solid nodules, cystic lesions containing a scolex or hydrocephalus.
- CT scan is more sensitive than MRI in identifying calcified lesions, while MRI is better for identifying cystic lesions and enhancement.
- CSF shows mononuclear pleocytosis and presence of eosinophils.
- In CSF, specific enzyme-linked immunoelectrodiffusion transfer blot (EITB) using lentil lectin purified glycoproteins is highly sensitive and specific.
- Histological examination of the excised subcutaneous nodule can establish a specific diagnosis.

Treatment

- For removal of the adult worm in the intestine, niclosamide (2 g as a single-dose) praziquantel (5 mg/kg) or albendazole may be used.
- Neurocysticercosis should be treated on the following lines:
  - Albendazole 15 mg/kg/day for 2–4 weeks is the drug of choice.
  - An alternative antiparasitic drug praziquantel (PZQ), can be used orally in a single day regimen of three doses of 25 mg/kg given at 2-hour intervals or the standard 15-day regimen of 50 mg/kg/day. Efficacy of a single day course is good in patients with a single cyst or low cyst burdens, but it is less efficacious in those with heavier cyst burdens.
  - Prednisolone 10 mg 8 hourly is given for 14 days, starting 1 day before the albendazole or PZQ.
  - Antiepileptic drugs should be given until the reaction in the brain has subsided.
  - Operative intervention may be required for internal hydrocephalus.

Q. Discuss briefly about hydatid disease.

- Hydatid disease is a tissue infection of humans caused by the larval stage of *Echinococcus granulosus*. Canines (especially dogs) are the definitive hosts for *E. granulosus*. Sheep and cattle are the common intermediate hosts. Hence, this form of disease has its highest incidence in countries where sheep and cattle-raising is carried out and population of dogs is high. Man is infected accidentally.
- The adult *E. granulosus* is a small worm measuring 5 mm in length that resides in the jejunum of canines for 5–20 months. In addition to the scolex and neck, it has three proglottides. The gravid segment splits to release eggs that are ingested by an appropriate intermediate host. The embryos escape from the eggs, penetrate the intestinal mucosa and enter the portal circulation. Most are filtered out by the liver and lungs, but some escape into general circulation to involve brain, kidney and other tissues. Those larvae develop into hydatid cysts. When the hydatid cyst is ingested by a canine the life cycle is complete.

- The hydatid cysts are unilocular, fluid-filled, distended cysts with an external pericyst, a middle laminated layer and an internal germinal layer. Brood capsules and second and third-generation daughter cysts develop from the germinal layer. "Hydatid sand" found in the cyst consists of scolices liberated from ruptured brood capsules. The hydatid fluid is highly antigenic.

Clinical Features

- Humans may ingest the eggs while handling a dog or drinking contaminated water. Usually, a latent period of 5–20 years occurs before diagnosis.
- In 75% of the patients with hydatid disease, the right lobe of the liver is involved and it contains a single cyst. These hepatic lesions often present as palpable masses or abdominal pain.
  - Obstruction of bile duct may result in obstructive jaundice.
  - Intrabiliary extrusion of calcified hepatic cysts can present with recurrent cholecystitis.
  - Rupture of a hydatid into the bile duct, peritoneal cavity, lung, pleura or bronchus may produce fever, pruritus, urticarial rash or an anaphylactoid reaction that may be fatal.
- A pulmonary hydatid may rupture producing cough, chest pain or haemoptysis.
- Central nervous system involvement may produce epilepsy or blindness.
- The disease can rarely involve heart, kidneys, spleen, ovary and thyroid.

Diagnosis

- Routine radiographs may pick up hydatid cysts. Pulmonary lesions are seen as round, irregular masses of uniform density. The "meniscus sign" or "crescent sign" is characterised by the presence of air between the pericyst and the laminated membrane. The "water lily sign" represents an endocyst floating in a partially fluid-filled cyst. Occasionally, a chest radiograph may show smooth rim of calcified hepatic cyst.
- CT scan and ultrasonography can detect the hydatid lesions by showing scolices and daughter cysts.
- The skin test (Casoni's test) may be positive (not routinely available).
- Complement fixation, immunofluorescent tests and ELISA to detect antibodies are positive in 70–90% of cases.
- Specific echinococcal antigens by immunoblot assays for confirmation (rarely required).

Treatment

- Surgical excision of the cysts is the treatment of choice.
- In inoperable cases, "high-dose" albendazole (7.5 mg/kg twice daily) should be given for 1–3 months.
- In selected cases, *p*ercutaneous *a*spiration, *i*nfusion of scolicidal agents (e.g. 95% ethanol or hypertonic saline) and *r*easpiration (PAIR) can be done. It is followed by albendazole treatment for 1 month.

Q. Write a short note on enterobiasis, pinworm infection or threadworm infection.

- Enterobiasis is an intestinal infection of humans caused by *Enterobius vermicularis*. The adult female averages 10 mm in length and the male 3 mm. They are seen in the caecum, appendix and the adjacent parts of the colon. The gravid female migrates through the anal canal at night, deposits her eggs on the perianal skin and dies. As many as 15,000 eggs may be laid in one night. These eggs are ingested and the larvae are released in the small intestine. The larvae migrate down the bowel lumen to reach the caecum and develop into adult worms.

Clinical Features

- Humans are usually infected by the direct transfer of eggs from the anus to the mouth by way of contaminated fingers. "Retroinfection" occurs when the eggs hatch in the perianal area and the larvae migrate back into the bowel lumen.
- The most common symptom is perianal itching (pruritus ani), especially at night, being related to the migration of the gravid female.
- Other symptoms include irritability, insomnia and enuresis.
- Migration of adult worm into the female genital tract may result in vaginal discharge, salpingitis and endometritis.

Diagnosis

- Directly visualising the worms in the perineal area.
- Stool examination for eggs (positive in only 5–10% cases).
- "Cellophane tape test".

- This test consists of touching cellophane tape to the perianal area several times, removing it and examining the tape under direct microscopy for eggs.
- The test should be conducted right after awakening on at least 3 consecutive days.
- This technique can increase the sensitivity to roughly 90%.

Treatment

- Two highly satisfactory drugs are available. Pyrantel pamoate given in a single oral dose of 11 mg/kg is the treatment of choice. Alternatively, a single oral dose of mebendazole 100 mg may also be used. Albendazole in a single-dose of 400 mg may also be given. Both are to be repeated once after 2 weeks.
- Where infection constantly recurs in a family, each member should be treated with mebendazole 100 mg twice daily for 3 days and repeated after 2 weeks. During this period all night clothes and bed linen are laundered and finger nails must be scrubbed before meals.

Q. Give a brief account of ascariasis or roundworm infection.

- Ascariasis is an infection of humans caused by *Ascaris lumbricoides*. The pale yellow worm is 20–35 cm long.
- Man is infected by eating food contaminated with mature ova, which hatch in the duodenum to release the larvae. The larvae migrate through the wall and are carried by bloodstream or lymphatics to the lungs. From the lungs the larvae ascend the bronchial tree, trachea and epiglottis and are swallowed. These are then mature in the small intestine to become adult worms.

Clinical Features

- Ascaris bronchopneumonia characterised by fever, cough, dyspnoea, wheeze, eosinophilic leucocytosis and migratory pulmonary infiltrates may occur during the stage of larval migration through the lungs.
- The adult worm may be vomited or passed in the stool.
- Heavy infections may be associated with abdominal pain and malabsorption of fat, protein, carbohydrate and vitamins.
- Bolus of worms may result in volvulus, intussusception or intestinal obstruction.
- The adult worms may migrate into appendix, bile ducts or pancreatic ducts, causing appendicitis, cholangitis, liver abscess or pancreatitis.
- Diagnosis is by demonstrating typical eggs in the stools. In heavily infected patients large collections of worms may be detectable on plain radiograph of the abdomen as a mass which produces contrast against the gas in the bowel ("whirl-pool" effect).

Treatment

- Ascaris bronchopneumonia is treated symptomatically. Severe cases may require steroids.
- Pyrantel pamoate given as a single oral dose of 11 mg/kg is effective in removing the adult worms from the intestine.
- Mebendazole given at a dose of 100 mg twice daily for 3 days or albendazole 400 mg (one dose) are also effective.
- The older agent, piperazine citrate is highly effective and less expensive, but slightly more toxic.

Q. Describe briefly about trichuriasis?

Q. Write a short note on whipworm infection.

- Trichuriasis is an intestinal infection of humans caused by *Trichuris trichiura*.
- The adult worms are found in the large intestine. They are 30–50 mm in length, with anterior two-thirds as a thread and posterior one-third as stouter, giving them a whip-like appearance ("whipworm"). The female produces the eggs that are passed in the stool. The eggs must incubate at least 3 weeks in the soil before they become infective. The ingested eggs hatch in the small intestine and release the larvae. The larvae migrate to the large intestine (mostly caecum) where they mature into adult worms.

Clinical Features

- Petechiae are seen at worm attachment sites in the intestine. On an average the patient loses 0.005 mL blood/worm/ day.
- The clinical manifestations include growth retardation, persistent diarrhoea, anaemia and abdominal pain.
- Trichuris dysentery syndrome is an even more serious manifestation of heavy whipworm infection, resulting in chronic dysentery and rectal prolapse.

Diagnosis

- Diagnosis is by demonstration of eggs in stools.
- Proctoscopy or colonoscopy can be performed and frequently demonstrates adult worms protruding from the bowel mucosa.

Treatment

- Mebendazole given at a dose of 100 mg twice daily for 3 days or albendazole 400 mg once day for 3 days is the treatment of choice. The dose may have to be repeated in patients with heavy infections.

Q. Describe ancylostomiasis or hookworm disease.

- Hookworm disease is a symptomatic infection caused by *Ancylostoma duodenale* or *Necator americanus*. It is one of the main causes of anaemia in the tropics.
- *Ancylostoma duodenale* or old world hookworm is found in Europe, Africa, China, Japan, India and the Pacific islands. *Necator americanus* or new world hookworm is found in Americas and the Caribbean.
- *Ancylostoma duodenale* adult worms are about 1 cm long and inhabit the upper part of the human small intestine, where they attach to the mucosa by means of the mouth parts and suck blood. Each adult extracts about 0.15 mL blood daily. The adults migrate within the small intestine and each site of attachment persists temporarily as a bleeding point. Following fertilisation, the female liberates about 20,000 eggs/day that are passed in the stool.
- *Necator americanus* is smaller in size, deposits fewer eggs and sucks less blood (0.03 mL/worm/day).
- The life cycles of the hookworms are similar. The eggs in the soil develop into rhabditiform larvae and later filariform larvae that penetrate the skin to enter vessels that carry them to the lungs. The larvae leave the alveolar capillaries, enter the alveoli, ascend the respiratory tree, enter the pharynx and are swallowed. In the intestine they develop into adult worms.

Clinical Features

- Itching dermatitis ("ground itch dermatitis") occurs at the site of entry of the larvae. The lesions are maximum on the feet, particularly between the toes.
- The larval migration through the lungs causes cough with blood-tinged sputum, fever and patchy pulmonary consolidation.
- A variety of gastrointestinal symptoms are common. These include vague epigastric discomfort or typical ulcer pain, abdominal distension, pica, vomiting and small frequent loose stools.
- The major clinical manifestations of hookworm disease are those of iron deficiency anaemia and hypoalbuminaemia consequent to chronic intestinal blood loss.
- Young children often have extreme anaemia, with cardiac insufficiency and anasarca.
- Older children may show retarded physical, mental and sexual development.
- In the adults there may be lassitude, dyspnoea, palpitation, tachycardia, constipation and pallor of skin and mucous membranes.

Diagnosis

- The characteristic eggs can be demonstrated in the stool by microscopic examination. The eggs of both worms are 60–70 μm in length and bounded by an ovoid transparent hyaline membrane; they contain two to eight cell divisions.
- The stools seldom contain gross blood, but tests for occult blood are usually positive.
- A peripheral blood eosinophilia as high as 70–80% may be seen in some cases.
- Haemoglobin level is usually low and anaemia is characteristically hypochromic and microcytic.
- Hypoalbuminaemia is a common finding in severe disease.

Treatment

- Improvement of nutrition with a high-protein diet.
- Anaemia should be treated with oral iron or blood transfusions. Mild anaemia usually responds to oral iron therapy. Severe anaemia is often associated with anasarca and this should be treated carefully with blood transfusions.
- The drugs currently favoured for the treatment of hookworms are mebendazole, albendazole and pyrantel pamoate. Mebendazole is given at a dose of 100 mg twice daily for 3 days. Albendazole requires single-dose of 400 mg. Pyrantel pamoate is given as a single oral dose of 11 mg/kg. Confirm eradication with follow-up stool examination 2 weeks after discontinuation of treatment. Ivermectin has poor efficacy against hookworm and is not recommended.

Q. Explain briefly about cutaneous larva migrans (creeping eruption).

- Cutaneous larva migrans are creeping eruptions caused by the larvae of *Ancylostoma braziliense* and *A. caninum* whose eggs are found in dog and cat faeces. *Strongyloides stercoralis* may also produce creeping eruptions known as larva currens (reflecting fast movement of strongyloides larva).
- The larvae that are present in soil penetrate the intact skin to enter the subcutaneous tissues. In the subcutaneous tissues, they cause multiple, intensely pruritic, serpiginous tracts that progress forwards. At the anterior end of the eruption the larva is present and a bleb may form.
- The main affected areas are the dorsum and sole of the feet, buttocks, pelvic waist, legs and shoulders.
- Infestation is usually self-limited that can persist for a few days to months, but rarely for years.
- Loeffler's syndrome (transient migratory pulmonary infiltrates, peripheral blood eosinophilia and sputum eosinophilia) is observed in many cases of larva migrans.

Treatment

- Ivermectin is the drug of choice. Dose is 150– 200 µg/kg as a single-dose.
- Alternative drug is albendazole (200 mg twice a day for 5–7 days).
- Local application of 15% thiabendazole cream for 7 days is as effective as ivermectin.
- Antihistamines may be of value in intense itching.

Q. Discuss clinical features, diagnosis and treatment of strongyloidiasis.

- Strongyloidiasis is an intestinal infection of humans caused by *Strongyloides stercoralis*.
- The adult worms are tiny and measure 2 mm in length. They reside in the upper part of jejunum. The adult female lays her eggs in the mucosa of jejunum. The eggs hatch and release the rhabditiform larvae, which are passed in the stools. In the soil, the rhabditiform larvae develop into the infective filariform larvae. The filariform larvae penetrate the skin of humans and are carried by bloodstream to the lungs. In the lungs, they ascend the respiratory tree, enter the pharynx and are swallowed. On reaching, the jejunum these larvae mature into the adult worms. This cycle is known as the direct host–soil–host cycle.
- In the indirect cycle, the rhabditiform larvae develop into free-living adult worms that reside in the soil. These free-living adults reproduce sexually to produce filariform larvae that initiate a new human cycle.
- In the autoinfection cycle, the rhabditiform larvae develop into filariform larvae before they are passed in the stool. They may then invade the intestinal mucosa or perianal skin of the same host without first going through a soil phase. This can lead to tremendously increased number of worms ("hyperinfection"). This is seen in patients with HIV infection and in patients taking corticosteroids.

Clinical Features

- The larval migration through skin may produce itchy rashes (ground itch).
- The larval migration through lungs produces cough, dyspnoea, haemoptysis and bronchospasm.
- The adult worms in the intestine may produce abdominal pain, bloating, diarrhoea, steatorrhoea and weight loss.
- Autoinfection may cause urticarial wheals across abdomen and buttocks (larva currens).
- Strongyloides hyperinfection occurs when patients chronically infected with *S. stercoralis* become immunosuppressed, or if immunosuppressed patients develop acute strongyloidiasis. This results in uncontrolled proliferation of larvae with dissemination to other organs, including lungs, liver, and brain. This may cause diarrhoea, pneumonia, meningo-encephalitis and death. Bacterial and fungal infections often occur because of leakage of gut flora from the bowel damaged by moving larvae. The enteric bacteria are also carried by invasive larvae on their outer surfaces that can result in septicaemia.

Diagnosis

- Stool examination for larvae (at least three samples).
- Eosinophilia in some patients.
- Examination of duodenal aspirate for larvae.
- ELISA for detecting IgG antibody to *S. stercoralis*.
- In patients with disseminated infection, stool tests, ELISA and sputum and blood examination for larvae.

Treatment

- The drug of choice is ivermectin (200 µg/kg/day) for 2 days.
- An alternative but less effective drug is albendazole, given orally at a dose of 400 mg twice daily for 7 days.

- In disseminated systemic infections, both ivermectin and albendazole should be given and may be continued for 7 days or till the parasites are cleared.

Q. Describe briefly about lymphatic filariasis and bancroftian filariasis.

- Filariasis is a group of disorders caused by infection with thread-like nematodes belonging to the family *Filariidae*. They invade lymphatics, and subcutaneous and deep tissues of humans. Filariasis includes the following conditions:
  - Lymphatic filariasis caused by *Wuchereria bancrofti* and *Brugia malayi*.
  - Loiasis caused by *Loa loa*.
  - Onchocerciasis (river blindness) caused by *Onchocerca volvulus*.

Lymphatic filariasis

Pathogenesis

- Lymphatic filariasis is caused by *Wuchereria bancrofti* and *Brugia malayi*. These nematodes are conveyed to humans by the bites of infected mosquitoes of a number of different species, the most common being *Culex fatigans* in *W. bancrofti* infection and *Mansonioides* in *B. malayi* infections.
- The adult worms live in the lymphatics of humans. The females produce microfilariae that circulate in large numbers in the peripheral blood at night. In the mosquito the ingested microfilariae develop into infective larvae.
- In humans, the microfilariae are present chiefly in the capillaries of the lungs and cause pulmonary eosinophilia. The presence of adult worms in the lymphatics causes allergic lymphangitis. Recurrent episodes of allergic lymphangitis lead to intermittent lymphatic obstruction (obliterative lymphangitis) and transient lymphoedema, which may later become permanent in the leg (elephantiasis), arm, genitalia or breast. Increased lymphatic pressure may cause retrograde flow of lymph or rupture of lymphatics causing chyluria, chylous ascites and chylous pleural effusion.
- Filarial nematodes contain endosymbiotic bacteria, *Wolbachia*. These are essential in worm fertility and survival. Doxycycline depletes *Wolbachia* from the worms and leads to long-term worm sterility and macrofilaricidal activity.

Clinical Features

Acute Dermato-Adeno-Lymphangitis (ADLA)

- Associated with fever and chills.
- Affected area usually in the extremities is extremely painful, warm, red, swollen and tender.
- Draining lymph nodes in the groin or axilla become swollen and tender.
- There may be lymphangitis, lymphadenitis, cellulitis or abscess.
- Entry of bacteria through the lesions of the affected parts is responsible.

Acute Filarial Lymphangitis

- Lymphangitis manifests as pain, tenderness and erythema along the course of inflamed lymphatics.
- The inguinal lymph nodes may become enlarged, painful and tender.
- Not associated with fever, toxaemia or evidence of secondary bacterial infection.

Acute Epididymo-Orchitis and Funiculitis

- Characterised by severe pain, tenderness and swelling of scrotum usually with fever and rigor.
- Testes, epididymis or the spermatic cord may become swollen and extremely tender.
- Also precipitated by secondary infections.

Chronic Stage

- Characterised by permanent lymphoedema ("elephantiasis") of legs, scrotal oedema, hydrocele, chylous ascites, chylous pleural effusion and chyluria.

Investigations

- In the early stages of lymphangitis there may be peripheral blood eosinophilia. Microfilariae are not seen in the peripheral blood.
- By about 1 year from the time of infection, microfilariae can be demonstrated in the peripheral blood at night.
- Microfilariae are usually present in the hydrocele fluid that may occasionally contain an adult worm.
- "Diethylcarbamazine (DEC) provocation test" involves the administration of 100 mg DEC that usually produces positive blood specimens within 30–60 minutes.
- Calcified filariae may sometimes be demonstrable by radiography.

- Serological tests demonstrating antibodies against filarial antigens are non-specific.
- Antigen detection in the blood by ELISA or immunochromatic method is highly sensitive and specific for *W. bancrofti*.
- PCR for DNA detection.
- Radionuclide lymphoscintigraphy to detect widespread lymphatic abnormalities.

Treatment

- DEC 6 mg/kg in three divided doses for 12–21 days kills microfilariae and adult worms.
- Ivermectin is effective in killing microfilariae, but not the adult worms.
- Doxycycline 200 mg per day for 4 weeks plus ivermectin as a single-dose (200 µg/kg).
- Antihistamines and corticosteroids may be necessary to control allergic phenomena.
- Surgery may be of use in established elephantiasis.

Control

- Mass administration of DEC 6 mg/kg as single-dose along with 400 mg of albendazole once in a year in highly endemic areas.

Q. Give a brief account of tropical pulmonary eosinophilia.

- This represents an atypical host response to various filariae including *W. bancrofti* and *B. malayi*. The antigens released when these parasites are destroyed initiate an immediate IgE-mediated reaction. The eosinophilic inflammatory reaction, over time, progresses to granuloma formation and fibrosis. In children, there may be marked enlargement of lymph nodes and spleen (Meyers–Kouwenaar syndrome), whereas in adults, cough, nocturnal bronchospasm and miliary pulmonary infiltrates are seen (Weingarten syndrome or tropical pulmonary eosinophilia).
- Can progress to interstitial fibrosis.

Diagnosis

- History of prolonged residence in an endemic area.
- Lack of microfilariae in the peripheral blood despite repeated examinations.
- Peripheral blood eosinophilia in excess of 3000/mL.
- High titres of filarial antibodies.
- IgE levels of at least 1000 units/mL.
- Therapeutic response to DEC within 7–10 days of initiating therapy (the drug is continued for 2 weeks).

Q. Write a short note on gonorrhoea.

Q. What is acute gonococcal urethritis?

- Gonorrhoea, a sexually transmitted disease (STD) is due to the Gram-negative diplococcus, *Neisseria gonorrhoeae*, which infects columnar epithelium of urethra, endocervix, rectum, pharynx and conjunctivae.
- Although it usually remains localised to initial sites of infection, it can ascend to genital tract to cause pelvic inflammatory disease (PID) in females and epididymo-orchitis and prostatitis in males. Dissemination can result in bacteraemia.
- Transmission is by genital–genital, genital–anorectal, oro–genital or oro–anal contact or by mother-to-child transmission at birth.

Clinical Features

- In men, predominant presentation is of acute urethritis ("clap"). Incubation period is 2–7 days following exposure. Symptoms are urethral discharge and dysuria. On examination, there may be mucopurulent urethral discharge, which may be accompanied by erythema of the urethral meatus.
- In women, symptoms relate to endocervical and urethral infection and include increased or altered vaginal discharge, intermenstrual bleeding, dysuria and menorrhagia.
- Asymptomatic genital tract infection occurs up to 50% of women.
- Rectal and pharyngeal infections are usually asymptomatic.
- Gonococcal bacteraemia is uncommon and presents with skin lesions, fever, arthralgia, acute arthritis and tenosynovitis. Skin lesions initially appear as small vesicles that subsequently become pustules and develop a haemorrhagic base. Gonococcal arthritis is asymmetric and migratory.

- Acute perihepatitis (Fitz–Hugh–Curtis syndrome) is a rare complication of PID and is thought to occur through direct extension of *N. gonorrhoeae* from fallopian tube to liver capsule and peritoneum along the paracolic gutters. Patients present with sharp, pleuritic right upper quadrant pain.
- In neonates, perinatal transmission of gonorrhoea may produce ophthalmia neonatorum.

Diagnosis

- Sterile pyuria—i.e. leucocyturia that accompanies a negative urine culture report.
- Gram's stain and culture of urethral, genital, rectal, pharyngeal or ocular secretions.
  - When collecting specimens in males with urethritis, any discharge present at the meatus can be easily recovered for examination. If no discharge is present at the meatus, urethral material must be recovered by inserting and rotating a small swab 2–3 cm into the urethra.
  - Nucleic acid amplification tests (NAATs) are generally more sensitive than culture. They can be used on urine samples and on swabs from endocervix, urethra, rectum and pharynx.
  - Fluorescein-conjugated monoclonal antibodies by direct fluorescence microscopy to detect antigen.
  - Enzyme-linked immunoassays for the detection of gonococcal antigen.
  - Blood cultures in disseminated disease.

Treatment

- Penicillin, tetracycline, ampicillin and quinolone resistance is quite frequent, and hence, should not be used to treat gonococcal infections.
- One of the following regimens is recommended at present:
  - Cefixime 400 mg orally (single-dose)
  - Ceftriaxone 250 mg intramuscularly (single-dose)
  - Spectinomycin 2 g intramuscularly (single-dose)
- If quinolone and azithromycin resistance is not a problem:
  - Ciprofloxacin 500 mg orally (single-dose)
  - Ofloxacin 400 mg orally (single-dose)
  - Levofloxacin 250 mg orally (single-dose)
  - Azithromycin 2 g orally (single-dose)
- For epididymo-orchitis, doxycycline 100 mg twice daily for 14 days along with one dose of ceftriaxone or ciprofloxacin.
- For disseminated gonococcal infection, ceftriaxone 1 g once a day or cefotaxime 1 g every 8 hours or spectinomycin 2 g every 12 hours for 7 days.
- Co-infection with *Chlamydia trachomatis* is common in young, heterosexual patients with gonorrhoea. Treatment for gonorrhoea should routinely be accompanied by effective treatment for Chlamydia infection (azithromycin 1 g as a single-dose or doxycycline 100 mg twice a day for 7 days).

Q. Discuss clinical features and treatment of chancroid.

Q. Explain briefly about bubo.

- Chancroid or soft chancre is an acute sexually transmitted infection characterised by painful genital ulcerations associated with inflammatory inguinal adenopathy. The responsible organism is *Haemophilus ducreyi*.
- Co-infection with *Treponema pallidum* and *Herpes simplex* in 10% cases.

Clinical Features

- Incubation period is usually 3–10 days.
- A small inflammatory papule appears on the external genitalia, which ulcerates within 2–3 days to give rise to the classic chancroidal ulcer. The classic chancroidal ulcer is superficial. The edge is ragged and undermined. The ulcer base is covered by a necrotic exudate. Chancroidal ulcer is painful and not indurated.
- Acute, painful, tender, inflammatory inguinal adenopathy occurs. The involved nodes become matted, forming a unilocular suppurative bubo. The overlying skin may rupture forming a single deep ulcer.
- Diagnosis is based on the isolation of *Haemophilus ducreyi* from an ulcer or bubo which appear as Gram-negative, slender rod or coccobacillus in a chain, the so called "school of fish" pattern.

Treatment

- Resistance to chloramphenicol, tetracyclines, ampicillin and sulphonamides is common.
- Effective regimens include:
  - Ceftriaxone 250 mg intramuscularly as a single-dose.
  - Azithromycin 1 g as a single-dose.
  - Erythromycin 500 mg four times a day for 7 days.
  - Ciprofloxacin 500 mg twice a day for 3 days.
- Sex partners of patients who have chancroid should be examined and treated, regardless of whether symptoms of the disease are present, if they had sexual contact with the patient during the 10 days preceding the patient's onset of symptoms.

Q. Describe in brief about Chlamydia infections.

Q. Write a short note on lymphogranuloma venereum (LGV).

- Chlamydia trachomatis is a sexually transmitted disease.

Clinical Features

- Asymptomatic.
- Trachoma.
- Urethritis, epididymitis, prostatitis, cervicitis and salpingitis.
- Untreated infection in men can cause infertility and reactive arthritis.
- Most women with *C. trachomatis* infection are typically asymptomatic; they are therefore more likely to develop complications from undiagnosed Chlamydia infection such as PID, infertility or ectopic pregnancy.
- Lymphogranuloma venereum (LGV) is a typical manifestation of *Chlamydia trachomatis*.
  - Primary genital lesion occurs from 3 days to 3 weeks after exposure. It is small, painless vesicle or non-indurated ulcer or papule located on the external genitalia.
  - Inguinal syndrome is characterised by painful inguinal lymphadenopathy beginning 2–6 weeks after presumed exposure. The inguinal lymphadenopathy is usually unilateral. The nodes are initially discrete that later become matted, fluctuant and suppurative. The overlying skin becomes fixed, inflamed and thinned. Finally, multiple draining fistulae develop. Extensive enlargement of inguinal lymph nodes above and below the inguinal ligament can occur ("groove sign").
  - Constitutional symptoms include fever, chills, headache, anorexia, meningismus, myalgias and arthralgias.

Diagnosis

- Isolation of the LGV strain of chlamydia from aspirated bubo pus, rectum, urethra, endocervix or from other infected tissue
- Frei skin test is of little value.
- Serological tests (e.g. microimmunofluorescence test and complement fixation test) to detect antibodies.
- Direct immunofluorescent antibody test to identify antigens associated with the bacteria in the smear.
- Nucleic acid probes and PCR to detect antigens.

Treatment

- Azithromycin 1 g as a single-dose or doxycycline 100 mg BID for 7 days.
- For LGV, doxycycline 100 mg BID for 3 weeks or erythromycin 500 mg QID for 3 weeks.
- Fluctuant buboes should be aspirated with a syringe and needle.

Q. Discuss granuloma inguinale (donovanosis).

- Granuloma inguinale is a genital ulcerative disease caused by the intracellular Gram-negative bacterium *Klebsiella granulomatis* (previously known as *Calymmatobacterium granulomatis*).

Clinical Features

- Presents as painless, progressive ulcerative lesions without regional lymphadenopathy.
- The lesions are highly vascular ("beefy red appearance") and bleed easily on contact. However, the clinical presentation can also include hypertrophic, necrotic or sclerotic variants.

- The causative organism is difficult to culture and diagnosis requires visualisation of dark-staining Donovan bodies on tissue crush preparation or biopsy using Wright stain.

Treatment

- Treatment stops the progression of lesions, although prolonged therapy may be required to permit granulation and re-epithelialisation of the ulcers.
- Treatment with antibiotics is required for at least 3 weeks.
- Effective regimens include:
  - Doxycycline 100 mg orally twice a day.
  - Trimethoprim–sulphamethoxazole one double-strength (800 mg/160 mg) tablet orally twice a day
  - Ciprofloxacin 750 mg orally twice a day.
  - Erythromycin base 500 mg orally four times a day.
  - Azithromycin 1 g orally once per week.

Q. Give a brief account of syphilis.

Q. Describe condylomata lata, mucous patches and snail track ulcers.

- Syphilis is a chronic systemic infection caused by *Treponema pallidum* and is usually sexually transmitted. Most cases are acquired by sexual contact with infectious lesions—i.e. the chancre, mucous patch, skin rash or condylomata lata. It may be transmitted through non-sexual modes also---i.e. transfusion or infection in utero.
- *Treponema pallidum* can rapidly penetrate intact mucous membranes or abraded skin. Within a few hours, they enter the lymphatics and bloodstream to produce systemic infection. The primary lesion appears at the site of inoculation. The generalised parenchymal, constitutional and mucocutaneous manifestations of secondary syphilis usually appear about 6–8 weeks after healing of the chancre.

Classification

Acquired syphilis	Congenital syphilis
- Primary syphilis - Secondary syphilis - Latent syphilis - Late syphilis (tertiary, quaternary)	- Early - Late - Stigmata

Primary Syphilis

- Primary chancre begins as a single painless papule that rapidly becomes an ulcerated and indurated lesion ("hard chancre"). The chancre is usually located on the penis in heterosexual males. In homosexual males, it may be seen in the anal canal, rectum or within the mouth. In females, the common primary sites are the cervix and the labia.
- Regional lymphadenopathy usually accompanies the primary lesion, appearing within 1 week of the onset of the lesion. The nodes are firm, rubbery, nonsuppurative, painless and non-tender. External genital and anal chancres produce bilateral inguinal lymphadenopathy. Chancres of cervix and vagina result in iliac or perirectal adenopathy.
- The primary chancre usually heals within 4-6 weeks (even without treatment), but the lymphadenopathy may persist for months.
- Primary syphilis in HIV-positive patients is often symptomless and these patients frequently present with secondary or latent infection.

Secondary Syphilis

- Secondary syphilis develops 6–8 weeks after the appearance of the primary chancre. It starts with symptoms of generalised infection like malaise, headache and low-grade fever. The four cardinal signs of secondary syphilis are:
  - Skin rashes (75%)
  - Generalised lymphadenopathy (50%)
  - Condylomata lata (10%)
  - Mucous patches (30%).
- Skin rashes start as macular lesions on the trunk and proximal limbs, progressing to a generalised papular rash. These lesions may progress to necrotic ulcers, which frequently involve the palms and soles.
- Generalised, firm, non-tender lymphadenopathy occurs in about 50% of cases.

- In warm, moist, intertriginous areas, including the perianal area, vulva, scrotum and inner thighs, papules enlarge and become eroded to produce broad, moist, pink or grey-white highly infectious lesions called condylomata lata.
- Mucous patches occur in the lips, oral mucosa, tongue, palate, pharynx, vulva, vagina or glans penis. The typical mucous patch is a superficial mucosal erosion surrounded by a red serpiginous periphery and is usually painless. Sometimes they may coalesce to form "snail track" ulcers.
- Other less common manifestations of secondary syphilis include meningitis, hepatitis, nephropathy (proteinuria, nephrotic syndrome or haemorrhagic glomerulonephritis), gastrointestinal involvement, ocular involvement (anterior uveitis, choroiditis, interstitial keratitis, retinal vasculitis, retinitis, optic neuritis, dacryoadenitis or scleritis), arthritis and periostitis.
- After several months, the secondary syphilis resolves to be followed by a latent period.

Latent Syphilis

- "Early latent" syphilis encompasses the 1st year after infection, while "late latent" syphilis, begins at 1st year after infection. A diagnosis of latent syphilis is established based on:
  - Positive specific treponemal antibody test for syphilis.
  - Normal CSF examination.
  - Absence of clinical manifestations of syphilis on physical examination and chest film.
  - History of primary or secondary lesions.
  - History of exposure to syphilis.
- Pregnant females with latent syphilis (particularly early latent) may infect the foetus in utero.
- About 70% of untreated patients never develop features of late syphilis; rest 30% of cases go on to develop late syphilis.

Late Syphilis

Asymptomatic Late Neurosyphilis

- The patient does not have any symptoms or signs.
- The CSF shows mononuclear pleocytosis and increased protein.
- VDRL is positive.
- Patients are at risk of developing symptomatic neurosyphilis and therefore, this condition requires treatment.

Tertiary (Benign Gummatous) Syphilis

- This takes 10 or more years to develop and affects skin, subcutaneous tissues, mucous membranes, submucosa, liver, spleen and bones. The characteristic feature is a granulomatous lesion called a gumma.

Quaternary Syphilis

- Quaternary syphilis includes cardiovascular syphilis and neurosyphilis.
- The manifestations of cardiovascular syphilis (e.g. aortitis) are discussed under "Diseases of the Cardiovascular System" and of neurosyphilis (e.g. meningovascular syphilis and tabes dorsalis) under "Diseases of the Nervous System".

Congenital Syphilis

Early Congenital Syphilis

- Manifestations appear within first 2 years of life, most often between 2 and 10 weeks of age. They resemble features of secondary syphilis.
- Rhinitis with blood-stained mucous or "snuffles".
- Mucocutaneous lesions including bullae, vesicles, mucous patches and condyloma lata.
- Bone involvement in the form of osteochondritis, osteitis and periostitis. Parrot pseudoparalysis occurs due to painful epiphysitis causing reluctance to move.
- Hepatosplenomegaly, lymphadenopathy, anaemia, jaundice and thrombocytopenia are important symptoms of early congenital syphilis.

Late Congenital Syphilis

- Occurs after 2 years of age.
- Remains subclinical in 50–60% cases.
- Interstitial keratitis, deafness, Clutton's joints, neurosyphilis, gummatous periostitis, destruction of palate and nasal septum.
- Cardiovascular involvement is rare.

Stigmata of Congenital Syphilis

- Hutchinson's teeth (centrally notched, widely spaced upper central incisors), mulberry molars (extra cusps on first molars), frontal bossing, saddle nose, saber chin (anterior tibial bowing).

Diagnosis

- In primary and secondary stages, *T. pallidum* may be demonstrable in the infectious lesions by dark-field microscopy that shows a drifting rotary motion (corkscrew).
- Direct fluorescent antibody *T. pallidum* (DFA-TP) test can detect *T. pallidum* in fixed smears prepared from suspect lesions.
- Demonstration of *T. pallidum* in tissues by appropriate stains.

Serologic Tests

Non-Treponemal Tests

- Used for screening.
- Measure both IgG and IgM antiphospholipid antibodies formed by the host in response to lipoidal material released by damaged host cells and lipid from the cell surfaces of the treponeme itself.
- Non-treponemal test antibody titres usually correlate with disease activity and results should be reported quantitatively. A fourfold change in titre is considered necessary to demonstrate a clinically significant difference between two non-treponemal test results that were obtained using the same serologic test.
- Non-treponemal tests usually become non-reactive with time after treatment; however, in some patients, these antibodies can persist at a low titre for a long period of time.
- The tests are:
  - Venereal Disease Research Laboratory (VDRL) test.
  - Rapid plasma reagin (RPR) test.

Treponemal Tests

- Used for confirmation.
- Most patients who have reactive treponemal tests will have reactive tests for the remainder of their lives, regardless of treatment or disease activity. However, 15–25% of patients treated during the primary stage revert to non-reactive after 2–3 years.
- Treponemal test antibody titres correlate poorly with disease activity and should not be used to assess treatment response.
- Various tests are:
  - Fluorescent treponemal antibody-absorption (FTA-ABS) test.
  - *T. pallidum* haemagglutination (TPHA) test.
  - *T. pallidum* immobilisation (TPI) test.

Management

Stage	Drug	Regimen
• Primary	Procaine penicillin	6,00,000 units IM once daily for 12 days
	Tetracycline	500 mg orally four times daily for 15 days
	Doxycycline	100 mg orally two times daily for 15 days
	Benzathine penicillin	2.4 million units IM single-dose (1.2 million units in each buttock)
• Secondary	Procaine penicillin	6,00,000 units IM once daily for 15 days
	Benzathine penicillin	2.4 million units IM single-dose
• Early latent	Benzathine penicillin	2.4 million units IM single-dose
• Late latent/tertiary	Benzathine penicillin	2.4 million units IM weekly for 3 weeks
• Cardiovascular	Benzathine penicillin	2.4 million units IM weekly for 3 weeks
• Neurosyphilis	Crystalline penicillin	18–24 million units/day for 10–14 days
	Procaine penicillin PLUS probenecid	2.4 million units/day IM for 10–14 day PLUS 500 mg QID for 10–14 day

- In primary, secondary and early latent syphilis, penicillin allergic patients should receive tetracycline or doxycycline for 2 weeks. In late latent syphilis, duration is 4 weeks.
- Ceftriaxone may also be used in a dose of 1 g once a day for 10–14 days. Azithromycin in a single-dose of 2 g is also effective except in men having sex with men and during pregnancy.
- A fourfold decrease in non-treponemal titres at 3 to 6 months is considered a satisfactory treatment response in all stages of syphilis.
- For neurosyphilis, follow-up should include lumbar puncture with CSF evaluation repeated every 6 months until the cell count is normal. If the cell count has not decreased after 6 months, retreatment should be considered.

Jarisch–Herxheimer Reaction

- It is an acute febrile reaction frequently accompanied by headache, myalgia and other symptoms that usually occurs within the first 24 hours after any therapy for syphilis.
- The Jarisch–Herxheimer reaction occurs most often among patients who have early syphilis.
- Antipyretics may be used, but they have not been proven to prevent this reaction.
- It may induce early labour or cause foetal distress in pregnant females. This concern should not prevent or delay therapy.

Chapter 18

Endocrine and Metabolic Diseases

Q. Describe the anatomy of pituitary gland.

- The pituitary gland is located in sella turcica, bridged over by diaphragma sellae.
- It is related to sphenoidal air sinuses below, optic chiasma above and cavernous sinuses laterally.
- The gland is composed of two lobes, the anterior lobe (adenohypophysis) and the posterior lobe (neurohypophysis).
- The pituitary gland is connected to hypothalamus by the infundibular stalk that carries portal vessels carrying blood from hypothalamus to the anterior lobe and nerve fibres to the posterior lobe.
- Conventional staining demonstrates three types of cells in the anterior lobe: acidophils, basophils and chromophobes.
- Electron microscopically, five distinct types of cells can be identified in the anterior pituitary, that secrete six different hormones. These are somatotrophs secreting GH, lactotrophs secreting prolactin (PRL), thyrotrophs secreting TSH, gonadotrophs secreting FSH and LH, and corticotrophs secreting ACTH.

Pituitary gland
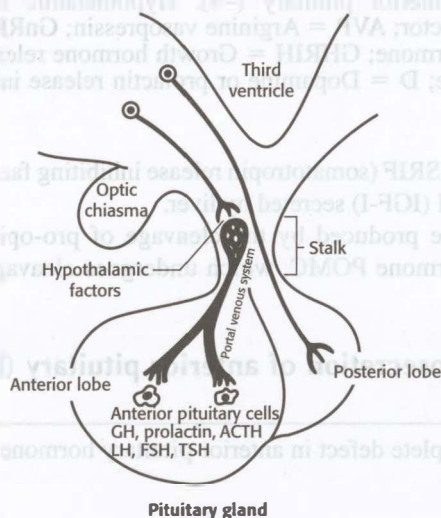
Q. Enumerate the pituitary hormones. Give their principal actions.

Hormone	Actions
Anterior pituitary hormones	
• Thyroid stimulating hormone (TSH)	Stimulates the production of thyroxine (T_4) and triiodothyronine (T_3)
• Luteinising hormone (LH), follicle stimulating hormone (FSH)	In males, both FSH and LH are necessary for spermatogenesis
	In males, FSH stimulates Sertoli cells to secrete androgen binding protein (ABP), transferrin, plasminogen activator and inhibin
	In males, LH stimulates Leydig cells to produce testosterone
	In females, FSH promotes growth and development of ovarian follicles during the follicular phase of menstrual cycle
	In females, the mid-cycle peak of LH (LH surge) induces ovulation
	In females, both FSH and LH are necessary for the development of corpus luteum during the luteal phase of menstrual cycle
• Growth hormone (GH)	Promotes growth

Hormone	Actions
• Prolactin (PRL)	Exerts its main effects on the breasts, stimulating lactation
• Adrenocorticotrophic hormone (ACTH)	Controls cortisol release from adrenal cortex and skin pigmentation
Posterior pituitary hormones	
• Arginine vasopressin (AVP)	Promotes reabsorption of water by renal tubules
• Oxytocin	Promotes uterine contraction and expression of milk from the breasts

Q. What are the hypothalamic hormones influencing the anterior pituitary? Give their principal effects.
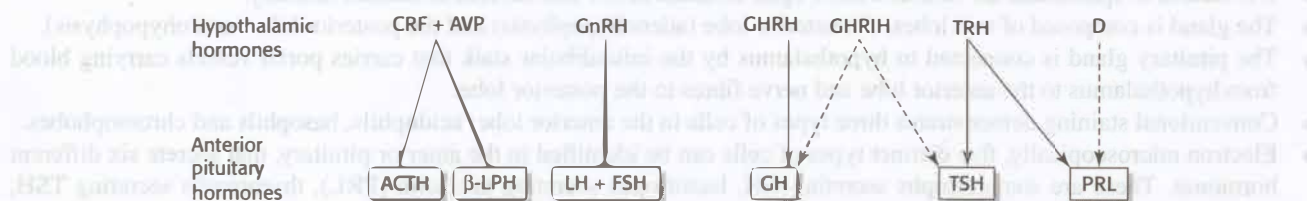
Hypothalamic hormones stimulating anterior pituitary ($\rightarrow$). Hypothalamic hormones inhibiting anterior pituitary ($\rightarrow$). CRF = Corticotrophin-releasing factor; AVP = Arginine vasopressin; GnRH = Gonadotrophin releasing hormone; GHRH = Growth hormone releasing hormone; GHRIH = Growth hormone release inhibitory hormone or somatostatin; TRH = Thyrotrophin releasing hormone; D = Dopamine or prolactin release inhibitory factor; β-LPH = β-Lipotropic pituitary hormone.

Note:
1. GHRIH is now called somatostatin or SRIF (somatotropin release inhibiting factor). Growth hormone produces its main effects via insulin-like growth factor-I (IGF-I) secreted by liver.
2. β-Lipotropin (β-LPH) is a hormone produced by the cleavage of pro-opiomelanocortin (POMC). The anterior pituitary gland produces the pro-hormone POMC, which undergoes cleavage to adrenocorticotropin (ACTH) and β-lipotropin.

Q. Give a brief account of hyposecretion of anterior pituitary (hypopituitarism and panhypopituitarism).

- Hypopituitarism is the partial or complete defect in anterior pituitary hormone secretion and may result from pituitary or hypothalamic disease.

Aetiology

• Congenital hypothalamic	Deficiencies of GnRH (Kallmann's syndrome), TRH, GHRH
• Acquired hypothalamic	Craniopharyngioma, sarcoidosis, tuberculosis, histiocytosis-X, surgery, radiotherapy, tumours, head trauma
• Pituitary	Pituitary adenoma, post-partum necrosis (Sheehan's syndrome), autoimmune (lymphocytic hypophysitis), surgery, radiotherapy, haemorrhage (pituitary apoplexy), empty sella syndrome, haemochromatosis

Clinical Features

- Clinical features depend on the underlying lesion.
- When hypopituitarism is secondary to pituitary tumours, symptoms related to mass effects (e.g. headache, visual impairment, diplopia, electrolyte alterations and disorders of the autonomic nervous system produced by hypothalamic involvement may be present).
- With progressive lesion (e.g. non-functioning pituitary tumours) there is a sequential loss of hormone secretion. Ultimately the patient goes into coma resulting from hypoglycaemia, water intoxication and hypothermia.

• GH deficiency	Earliest to occur, but no significant symptoms in adults. May produce an increased risk of fracture, a deranged cardiovascular risk profile (deposition of visceral fat, increased LDL and reduced HDL) and a decreased quality of life. In children, lower final height, decreased lean body mass and higher fat mass
• LH deficiency	Leads to loss of libido and impotence in males, and oligomenorrhoea or amenorrhoea, vaginal atrophy and hot flushes in females. Later, in males, there may be gynaecomastia and decreased frequency of shaving. In both sexes, infertility and osteoporosis occur, axillary and pubic hair becomes sparse, and the skin becomes finer and wrinkled
• ACTH deficiency	Leads to cortisol deficiency resulting in symptoms and signs of adrenal insufficiency (e.g. fatigue, weakness, dizziness, nausea, vomiting, hypotension, hypoglycaemia, weight loss) with skin pallor due to lack of melanin and normal plasma electrolytes (relative preservation of mineralocorticoid production)
• TSH deficiency	Leads to symptoms and signs of secondary hypothyroidism (tiredness, cold intolerance, constipation, weight gain, hair loss, dry skin, bradycardia, hoarseness, slow mental processes)
• PRL deficiency	Failure of lactation

- Lactotroph cells, unlike any other pituitary-cell lines, receive predominantly inhibitory signals from the hypothalamus; this inhibitory control explains increase in prolactin levels that result from either hypothalamic damage or hypothalamic–pituitary disconnection. However, when pituitary itself is damaged prolactin levels fall.
- Compared to primary adrenal insufficiency, ACTH deficiency does not cause salt wasting, volume contraction, and hyperkalaemia because it does not result in clinically important deficiency of aldosterone. Further, ACTH deficiency results in pallor of skin and not hyperpigmentation.

Laboratory Investigations

- Demonstration of low levels of trophic pituitary hormones in the setting of low-target hormones. However, sometimes, levels of trophic hormones may be normal.
  - Low free T_4 with low or inappropriately normal TSH.
  - Low early morning cortisol with low or inappropriately normal ACTH.
  - Low testosterone without elevation of gonadotrophins (LH and FSH).
  - Low IGF-I level (an indicator of GH deficiency).
- Provocation tests may be required to assess pituitary reserve. These include:
  - GH response to insulin-induced hypoglycaemia, L-dopa or combination of arginine and GHRH. Insulin-induced hypoglycaemia (also known as insulin tolerance test) is considered the gold standard test.
  - Prolactin level fails to rise after TRH.
  - ACTH response as assessed by measuring cortisol response to insulin-induced hypoglycaemia, CRH or metyrapone.
- TSH response to TRH.

Management

- ACTH deficiency is treated with cortisol 20 mg in the morning and 10 mg in the evening or prednisolone 5 mg in the morning and 2.5 mg in the evening. Doses should be at least doubled during acute illness and administered without delay by intramuscular or intravenous injection in patients who are vomiting.
- TSH deficiency is treated with T_4 0.1–0.15 mg daily with the aim of maintaining free T_4 in the upper quartile of normal range. T_4 should not be administered until adrenal function has been evaluated and either found to be normal or treated.
- Gonadotrophin deficiency is treated with sex hormone (testosterone or oestrogen-progestin) replacement, based on the age and sex of the patient. Men and women who wish to be fertile should be given gonadotropins.

Q. Discuss the differential diagnosis, investigations and management of short stature or dwarfism.

- Dwarfism is defined as a height that is more than 2 standard deviations below the mean for age, sex, and population.
- Most cases are due to normal variants in growth (familial short stature and constitutional delay of growth and puberty).

Differential diagnosis

• Familial (genetic) short stature	Low-normal growth velocity throughout life
• GH deficiency	Frontal bossing, central obesity, high-pitched voice
• Hypothyroidism	Dry skin, coarse hair, immature facies
• Cushing's syndrome	Central obesity, striae, hypertension
• Gonadal dysgenesis	Webbed neck, multiple pigmented naevi, shield chest, delayed sexual development
• Pseudohypoparathyroidism	Moon facies and obesity, short metacarpals, mental retardation
• Bone–cartilage dysplasia	Abnormal proportions, macrocephaly
• Russell–Silver dwarfism	Small at birth, pointed facies, asymmetry
• Other causes	Turner's syndrome, IUGR, premature birth, cyanotic congenital heart diseases, chronic liver, pulmonary or kidney disease, undernutrition, rickets, malabsorption, uncontrolled type 1 diabetes mellitus, idiopathic

Laboratory Investigations

Screening test	Disorder
• Bone age	Constitutional delay, hypothyroidism, GH deficiency
• Lateral skull film	Craniopharyngioma or other central nervous system lesions
• Serum calcium	Pseudohypoparathyroidism
• Serum phosphate	Vitamin D-resistant rickets
• Serum bicarbonate	Renal tubular acidosis
• Blood urea nitrogen (BUN)	Renal failure
• Calcium, alkaline phosphatase, iron, ferritin, albumin	Malabsorption syndrome
• Complete blood count	Anaemia, nutritional disorder
• ESR	Inflammatory bowel disease
• Chromosomal karyotype	Gonadal dysgenesis or other abnormalities
• Serum thyroxine	Hypothyroidism
• IGF-I*/SM-C	GH deficiency
• Antiendomysium antibodies, antitissue transglutaminase antibodies	Coeliac disease

*IGF-I—Insulin like growth factor-I; previously known as somatomedin-C (SM-C)

Treatment

- Treatment of underlying cause.
- Growth hormone may be of some benefit in children with idiopathic dwarfism.

Q. Describe Sheehan's syndrome.

- Sheehan's syndrome results from infarction of pituitary gland during post-partum period.
- Post-partum pituitary infarction occurs because the enlarged pituitary gland of pregnancy is more vulnerable to ischaemia of post-partum haemorrhage and systemic hypotension.
- Failure to lactate is the earliest symptom.
- Another typical symptom is failure to regain menstruation after delivery and breast involution.
- Other symptoms of hypopituitarism appear over months or years, though some patients present acutely.
- Uncommonly, it can present acutely with circulatory collapse, severe hyponatraemia, diabetes insipidus, hypoglycaemia, congestive cardiac failure, psychosis, finally leading to coma and death.
- Diagnosis is same as that for hypopituitarism (refer before). MRI may show hypertrophic pituitary in early stages, but later, atrophic pituitary and empty sella develop. It also excludes a pituitary mass.
- Treatment is substitution of deficient hormones.

Q. What is pituitary apoplexy?

- A rare but potentially life-threatening clinical syndrome resulting from acute haemorrhage or infarction of the pituitary gland.
- Presents with a sudden onset of headache, vomiting, visual disturbances (visual acuity impairment and visual field impairment) and decreased consciousness.
- It usually occurs in presence of a pituitary adenoma.
- Initial management consists of careful monitoring of fluid and electrolyte balance coupled with immediate replacement of deficient hormones, in particular corticosteroids.
- Surgical decompression may be required in those with progressive neuro-ophthalmic signs.

Q. What are the common pituitary tumours? Discuss briefly their clinical manifestations, investigations and management.

- Pituitary tumours may be microadenomas (less than 10 mm diameter) or macroadenomas (more than 10 mm diameter).
- They may be functional or non-functional. Some functional tumours may produce more than one hormone. Most non-functional tumours do produce intact gonadotropins or their glycoprotein subunits. Non-functional tumours found incidentally during MRI/CT examination or at autopsy are known as pituitary incidentalomas.

Common Pituitary Tumours

- Macroadenoma with GH hypersecretion.
- Microadenoma with ACTH hypersecretion.
- Prolactin-secreting adenoma (prolactinoma).
- Craniopharyngioma.
- Metastatic tumours.
- Part of multiple endocrine neoplasia type I (MEN-I), which includes parathyroid, pancreatic and pituitary (usually prolactinoma) tumours.

Clinical Features

- Due to hypofunction by pressure on surrounding normal pituitary tissue (see hypopituitarism).
- Due to involvement of neighbouring structures.
  - Dura—headache (commonest).
  - Optic chiasma, nerve or tract—visual field defects, loss of acuity and optic atrophy.
  - Cavernous sinus—III, IV and VI nerve palsies resulting in diplopia and strabismus, facial numbness.
  - Hypothalamus—obesity, disturbances of sleep, thirst, appetite and temperature regulation, and diabetes insipidus (DI).
  - Miscellaneous—anosmia (frontal lobe involvement), headache, vomiting, papilloedema (raised intracranial tension).
- Due to secretion of hormones.
  - GH—acromegaly or gigantism.
  - Prolactin—amenorrhoea, galactorrhoea and impotence.
  - ACTH—Cushing's syndrome.
  - TSH—hyperthyroidism.

Investigations

- Plain radiograph of the pituitary fossa may show one or more of the following abnormalities:
  - Enlargement of sella turcica.
  - Erosion of clinoid process.
  - Suprasellar calcification.
  - Double floor of the sella.
- CT scan with contrast enhancement—more sensitive than MRI for bony erosions and presence of calcification.
- Magnetic resonance imaging (before and after gadolinium)—more sensitive than CT scan for defining the soft tissue tumour.
- Visual field plotting can identify the site of lesion in some cases:
  - Optic chiasma—bitemporal hemianopia.
  - Optic nerve—unilateral loss of acuity or scotoma.
  - Optic tract—homonymous hemianopia.

- Functional assessment of the gland—e.g. hormonal assays.
  - Hormonal assays—PRL, IGF-I, 24-hours urinary cortisol, FSH, LH and thyroid function tests.

Treatment

- Drug therapy with dopamine agonists like bromocriptine and carbegoline is effective in prolactinomas. This can shrink the tumour and possibly avoid surgery.
- Somatostatin analogues including lanreotide and octreotide, are considered first-line medical therapy for growth hormone-producing tumours if surgery is not possible.
- Trans-sphenoidal or trans-frontal surgery enables removal of the tumour.
- Radiotherapy can suppress the tumour growth and reduce its secretory capacity. This can be achieved by external radiotherapy (fractionated) or gamma knife or a modified linear accelerator. Gamma knife (stereotactic radiosurgery) involves precise delivery of large single high-energy dose directly to the tumour under stereotactic surgery.

Q. Describe the clinical features, diagnosis and management of acromegaly.

Aetiology

- GH hypersecretion occurring in adult life after epiphyseal closure results in acromegaly (excess before epiphysis closure results in gigantism).
- Pituitary tumour (somatotroph pituitary adenoma) is the most common cause. Some adenomas are mixed that secrete GH as well as prolactin.
- Rare causes include excessive GH secretion from pancreatic islet cell tumour, or excessive secretion of GH-releasing hormone from hypothalamic lesions, bronchial carcinoid and small cell lung carcinoma.

Clinical Features

- Soft tissue changes	Thickening of skin, increased skin tags, acanthosis nigricans, increased sweat and sebum resulting in moist and oily skin, enlargement of lips, nose and tongue, increased heel pad thickness, visceral enlargement—e.g. thyroid, heart and liver, carpal tunnel syndrome, myopathy, sleep apnoea, Raynaud's phenomenon
- Bone changes	Large spade-like hands, large feet, prognathism, prominent supraorbital ridges, large frontal sinuses, wide-spacing of the teeth, arthropathy, kyphosis, osteoporosis
- Metabolic effects	Glucose intolerance or clinical diabetes mellitus
- Pressure effects	Refer pituitary tumour
- Cardiac effects	Coronary heart disease, cardiomyopathy, hypertension, left ventricular hypertrophy
- Others	Increased risk of colonic polyps and carcinoma

Investigations

- Investigations of pituitary tumour (refer pituitary tumour).
- Elevated IGF-I levels.
- GH levels are measured during an oral glucose tolerance test (OGTT). A failure of suppression or a paradoxical rise of GH indicates acromegaly.

Treatment

Surgery

- Trans-sphenoidal surgical removal of adenoma is the treatment of choice.

Medical Therapy

- Primary treatment with drugs is indicated in:
  - those with no risk of visual impairment from the tumour.
  - those who are poor candidates for surgery; those who decline surgery.
  - those with tumours unlikely to be controlled by surgery.
  - those who require the preservation of intact pituitary function (especially fertility).

- Various drugs are:
  - Bromocriptine or cabergoline (dopamine receptor agonists) are useful in those with mildly elevated IGF-I.
  - Octreotide or lanreotide (somatostatin analogues). Somatostatin analogues are more effective than dopamine agonists and act on pituitary somatostatin receptors to produce inhibition of GH and IGF-I.
  - Pegvisomant, a GH receptor antagonist, blocks peripheral IGF-I action in almost all patients, and is indicated in patients who are inadequately controlled with other modalities or in patients experiencing clinically significant drug side effects. Tumour size should be monitored at intervals, as the therapy is directed at blocking peripheral GH receptors and not at treating the pituitary tumour.

Radiotherapy

- External radiotherapy in patients not candidates for surgical therapy, and in whom medical therapy fails.
- Radiosurgery (gamma knife, cyber knife).

Others

- Treatment of diabetes, hypertension and hyperlipidaemia.

Q. Discuss prolactinoma and hyperprolactinaemia. Write briefly on their causes, clinical features, investigations and treatment.

- Prolactinoma is a pituitary tumour producing prolactin. Most of them are microadenomas.
- Hyperprolactinaemia means elevated levels of plasma prolactin.

Causes

• Physiological—e.g. pregnancy, lactation, sleep	• Chronic renal failure
• Pituitary tumours—e.g. prolactinomas	• Cirrhosis of the liver
• Hypothalamic and pituitary stalk diseases	• Drugs—e.g. dopamine receptor blockers (phenothiazines, metoclopramide), dopamine synthesis inhibitors (α-methyldopa), reserpine, opiates, cimetidine, oestrogens
• Primary hypothyroidism	

Clinical Features

- Galactorrhoea in both sexes.
- Amenorrhoea, oligomenorrhoea, menorrhagia and infertility in females.
- Loss of libido, impotence, infertility and gynaecomastia in males.
- A sufficiently large macroadenoma is usually associated with visual field defects and compression of other parts of pituitary (see pituitary tumours).

Investigations

- Raised plasma prolactin levels.
- Study of pituitary anatomy and assessment of the other pituitary functions (refer pituitary tumours).

Treatment

- Bromocriptine (2.5 mg thrice daily) or cabergoline; both are dopamine agonists. These agents reduce the secretion of prolactin as well as size of tumour. Cabergoline is preferred to bromocriptine.
- Trans-sphenoidal removal, if dopamine agonists do not help or there is a large, invasive tumour.
- External radiotherapy is rarely required. It may be considered in cases resistant to medical treatment and poor response to surgery.
- Asymptomatic patients who do not require restoration of pregnancy should be monitored regularly and given oestrogens to prevent bone loss.

Q. Give a brief account of diabetes insipidus (DI).

- Diabetes insipidus (DI) can be divided into following types:
  - Deficient production of ADH.

- Primary deficiency (neurogenic, pituitary, hypothalamic, cranial or central DI) occurs due to agenesis or destruction of neurohypophysis.
- Secondary deficiency occurs due to inhibition of ADH secretion (primary polydipsia).
- Deficient action of ADH (nephrogenic DI).

Aetiology

Primary deficiency of ADH	Secondary deficiency of ADH
• Severe head injury • Neoplasms • Craniopharyngioma • Pituitary adenoma • Meningioma • Metastatic • Lymphoma, leukaemias • Granulomas • Sarcoidosis • Histiocytosis • Infections • Chronic meningitis • Viral encephalitis • Inflammatory • Hypophysitis • Wegener's granulomatosis • Vascular • Sheehan's syndrome • Hypoxic encephalopathy • Genetic defects (autosomal dominant or recessive, X-linked) • Idiopathic	• Psychogenic polydipsia • Dipsogenic polydipsia (abnormal thirst) • Iatrogenic **Nephrogenic diabetes insipidus** • Drugs • Lithium • Demeclocycline • Amphotericin B • Aminoglycosides • Cisplatin • Rifampicin • Metabolic • Hypercalcaemia • Hypokalaemia • Obstructive uropathy • Amyloidosis • Vascular causes • Sickle-cell anaemia • Acute tubular necrosis • Genetic • Idiopathic

Clinical Features

- Polyuria, excessive thirst and polydipsia (with predilection for cold drinks) are the cardinal manifestations of DI.
- Daily urine output >50 mL/kg/day and may reach as high as 10–15 L.
- In traumatic DI triphasic response may be seen: initial polyuria, prolonged antidiuresis and final polyuria.

Diagnosis

- The urine is clear and of low specific gravity. The osmolality is low, usually less than that of plasma. However, in primary polydipsia, plasma osmolality may be lower than urinary osmolality.
- Serum sodium is borderline high indicating water loss.
- Water deprivation test (see below).
- MRI of pituitary and hypothalamus.

Diagnosis of DI by Water Deprivation Test

- The diagnosis of cranial DI depends on demonstrating that a rise of plasma osmolality induced by withholding fluids is not accompanied by a normal rise in the osmolality (to 1000–1200 mOsm/L) or specific gravity of urine; but that when vasopressin is given such a rise does occur. The latter test is necessary to show that kidney is capable of concentrating the urine that it cannot do in nephrogenic DI. In dipsogenic polydipsia, urinary osmolality rises appropriately during fluid restriction.

Treatment

- Desmopressin (DDAVP—1-deamino-8-D-arginine vasopressin) 10–20 μg intranasally once or twice a day.
- Chlorpropamide enhances the renal responsiveness to vasopressin. Hypoglycaemia can be a problem.
- Carbamazepine is an alternate drug with similar action.
- Thiazide diuretics (e.g. bendrofluazide) are the only effective drugs for nephrogenic DI.

Q. What are the various thyroid function tests? Explain.

- The hormones secreted by thyroid gland are T_3, T_4 and calcitonin.

Thyroid Function Tests

Serum TSH

- Measured by immunoradiometric assays (TSH IRMAs).
- Most sensitive index of thyroid function.
- Suppressed levels indicate primary thyrotoxicosis.
- Elevated levels indicate primary hypothyroidism.
- Besides primary thyroid disease, TSH levels may also vary in certain other conditions. Therefore, TSH value should always be interpreted along with T_4 assay. These conditions include:
  - Severe non-thyroidal illness (sick euthyroid syndrome).
  - TSH-secreting pituitary tumours.
  - First trimester of pregnancy (low TSH).
  - High doses of corticosteroids (low TSH).
  - Secondary hypothyroidism caused by hypothalamic–pituitary disease may produce low, normal or normal–high levels that are inappropriate for the very low free T_4 level.

TRH Test

- Plasma TSH levels are measured before and after intravenous administration or TRH.
- Failure of plasma TSH level to rise indicates primary thyrotoxicosis.
- This test is not used nowadays as sensitive TSH assays are available.

Serum Free T_3 (fT_3) and Free T_4 (fT_4)

- Advantage over the measurement of total T_3 and T_4 is that these are not influenced by changes in the thyroid hormone binding globulins (TBG), prealbumin and albumin.
- In patients with primary thyrotoxicosis, fT_3 and fT_4 levels are elevated.
- In patients with T_3-thyrotoxicosis, fT_4 levels are normal and fT_3 levels are raised.
- In patients on T_4 therapy, fT_4 levels are raised and fT_3 levels are normal.

Total Serum Thyroxine (tT_4)

- Altered by factors that affect the concentration of TBG.
- Raised levels are characteristically seen in hyperthyroidism; also during pregnancy, oestrogen therapy, tamoxifen use and as a congenital anomaly.
- Depressed levels are characteristically seen in hypothyroidism; also with nephrotic syndrome, androgen therapy, liver failure, or drugs like salicylates, sulphonylureas and phenytoin.

Total Serum Triiodothyronine (tT_3)

- Subject to the same limitations as for tT_4 in relation to TBG.

Reverse T_3 (rT_3)

- Reverse T_3 (rT_3) is principally a product of T_4 degradation in peripheral tissues. It is also secreted by the thyroid gland, but the amounts are insignificant.
- Elevated in subjects with high TBG.
- Normal in hypothyroid patients treated with thyroxine, indicating that peripheral T_4 metabolism is an important source of circulating rT_3.

Uptake of Radioactive Iodine or Technetium

- Overactive gland synthesising excess T_3 has an increased uptake of iodine. The increased uptake is demonstrated by giving an oral tracer dose of ^{131}I or ^{121}I and measuring the thyroid uptake after 4 hours, using a counter over the neck. Alternatively, technetium-99m (^{99m}Tc) may be given intravenously and the thyroid uptake is measured.
- Iodine deficiency or enzyme deficiency may show increased uptake measurement even in the absence of thyrotoxicosis.
- Excess iodine may show diminished uptake measurement even in the presence of thyrotoxicosis.
- Acute autoimmune thyroiditis may manifest as low iodine uptake thyrotoxicosis.

Radionuclide Scan

- Radionuclide scanning of thyroid using ^{131}I, ^{99m}Tc or ^{121}I is very useful in demonstrating the distribution of functioning thyroid tissue.
- It is extremely useful in determining the activity of a solitary thyroid nodule. A "hot" nodule indicates that it is functional, and a "cold" nodule indicates that it is non-functional.
- It is also useful to determine whether a goitre is multinodular or diffuse, retrosternal extension of thyroid and the nature of sublingual thyroid.

Tests to Determine Aetiology of Thyroid Disease

- In autoimmune thyroiditis, antibodies against thyroid peroxidase (TPO) and thyroglobulin (Tg) are present. These antibodies may also occur in normal population but these persons are at a high risk of developing thyroid disease late in life.
- Thyroid-stimulating immunoglobulins (TSI) are present in Graves' disease. These antibodies stimulate TSH receptors.
- Serum Tg levels are increased in all types of thyrotoxicosis except thyrotoxicosis factitia. Levels of Tg are also used to follow-up a patient with thyroid cancer.
- Calcitonin, secreted by parafollicular (C) cells, is increased in medullary thyroid carcinoma.
- Fine-needle aspiration cytology of thyroid nodule.

Q. Discuss the aetiology, clinical features, investigations and management of hyperthyroidism.

Q. Discuss the pathogenesis, clinical features, investigations and management of Graves' disease.

Causes

• Graves' disease	• Hydatidiform mole
• Multinodular goitre	• Choriocarcinoma
• Solitary thyroid nodule (toxic adenoma)	• Struma ovarii
• Excess pituitary secretion of TSH	• Carcinoma of thyroid
• Drugs (excess of iodine; amiodarone)	• Subacute thyroiditis

Pathogenesis

Graves' Disease

- TSI or TSH-receptor antibodies (TRAb) are IgG antibodies directed against the TSH receptors on the follicular cell, which stimulate thyroid hormone production and goitre formation.
- The ophthalmopathy and dermatopathy associated with Graves' disease is due to immunologically mediated activation of fibroblasts in the extraocular muscles and skin, with accumulation of glycosaminoglycans, leading to trapping of water and oedema initially. Later fibroblasts produce fibrosis.
- Genetic factors are significant in a minority of cases. HLA-DR3 is the best-documented risk factor.
- Viral or bacterial infections may trigger hyperthyroidism. *E. coli* and *Y. enterocolitica* possess cell membrane TSH receptors. The antibodies produced against these organisms cross-react with the TSH receptors, triggering the disease.
- Another immunoglobulin, a blocking antibody against TSH receptor, finally results in thyroid failure.

Treatment-Induced Hyperthyroidism

- Iodine-induced hyperthyroidism can occur after intake of excess iodine in the diet, exposure to radiographic contrast media or medications.
- It generally occurs in patients with an underlying autonomously functioning thyroid gland (caused, for example, by a nodule, multinodular goitre or Graves' disease). It can also occur in patients with endemic goitre who are treated with iodine. This is known as Jod–Basedow phenomenon.
- It is characterised by suppressed serum TSH level with normal circulating thyroid hormone levels.
- Paradoxically, excess uptake of iodine by the thyroid may inhibit thyroid hormone synthesis (Wolff–Chaikoff effect). Thus, iodide toxicity can eventually cause iodide goitre, hypothyroidism or myxoedema.
- The antiarrhythmic drug amiodarone has 37% iodine content with high tissue penetration and a half-life of months. The elemental iodine load of about 9 mg/day from a 200-mg tablet can precipitate hyperthyroidism if there is pre-existing goitre (type I: amiodarone-induced hyperthyroidism), while the drug itself causes thyroiditis in 5–10% of users, typically after about 2 years of therapy (type II: amiodarone-induced hyperthyroidism) that can later on lead to hypothyroidism.

- Factitial hyperthyroidism is caused by intentional or accidental ingestion of excess amounts of thyroid hormone. Some patients may take thyroid preparations to achieve weight loss.

Clinical Features of Thyrotoxicosis

• Thyroid	• Diffuse or nodular enlargement
• Gastrointestinal	• Weight loss, increased appetite, vomiting, increased stool frequency, diarrhoea, steatorrhoea
• Cardiorespiratory	• Exertional dyspnoea, exacerbation of asthma, palpitations, angina, sinus tachycardia, atrial fibrillation, wide pulse pressure, cardiac failure, cardiomyopathy
• Neuromuscular	• Nervousness, irritability, emotional lability, psychosis, fine tremors, hyper-reflexia, ill-sustained clonus, muscle weakness, proximal myopathy, bulbar myopathy
• Dermatological	• Increased sweating, pruritus, palmar erythema, spider naevi, onycholysis, alopecia, pigmentation
• Reproductive	• Menstrual disturbances (amenorrhoea or oligomenorrhoea), infertility, repeated abortions, loss of libido, impotence
• Miscellaneous	• Heat intolerance, fatigue, apathy, gynaecomastia, thirst

- Elderly patients with hyperthyroidism present with anorexia, apathy, and dominant cardiovascular and myopathic features. Younger patients with hyperthyroidism present with dominant neurological manifestations.

Graves' Disease

- Graves' disease is distinguished from other forms of hyperthyroidism by the presence of diffuse thyroid enlargement with or without bruit, ophthalmopathy and pretibial myxoedema.
- Vitiligo, finger clubbing and lymphadenopathy are common in Graves' disease.

Ophthalmopathy (Eye Signs)

- It is present in 50% of the patients when first seen, but may precede Graves' disease by many years (exophthalmic goitre or Graves' disease) or may develop even after successful treatment of Graves' disease.
- Pathogenesis of ophthalmopathy is not well understood. There is an increase in the bulk of orbital contents with a rise in retrobulbar pressure. This results in exophthalmos and optic nerve compression (congestive ophthalmopathy). Ocular myopathy is also seen.
- Symptoms include excessive lacrimation, grittiness, redness, diminution of visual acuity and diplopia.
- Signs include exophthalmos, corneal ulcers, chemosis, ophthalmoplegia, lid lag, lid retraction, visual field defects and papilloedema.
- Majority do not require any treatment. Various symptomatic measures include:
  - Methylcellulose eye drops for grittiness.
  - Tinted glasses to reduce lacrimation.
  - Lateral tarsorrhaphy for corneal ulcers.
  - Persistent diplopia is treated by surgical correction of extraocular muscles.
  - Papilloedema, loss of visual acuity and visual field defect require emergency treatment with prednisolone. If there is no response orbital decompression should be done.

Pretibial Myxoedema

- This is an infiltrative dermopathy typically affecting the anterior aspect of the leg extending on to the dorsum of the foot. Rarely, face and arms are affected.
- There are raised pinkish or purplish plaques that may be itchy. The skin may have a peau d' orange appearance with coarse hair.
- Pretibial myxoedema may be treated with local injections of triamcinolone or application of betamethasone ointment.

Other Disorders Associated with Graves' Disease

- Autoimmune disorders:
  - Endocrine: Addison's disease, type 1 diabetes mellitus, primary gonadal failure, hypophysitis, Hashimoto's thyroiditis.
  - Non-endocrine: coeliac disease, vitiligo, alopecia areata, myasthenia gravis, pernicious anaemia, immune thrombocytopenic purpura, rheumatoid arthritis.
- Others:
  - Hypokalaemic periodic paralysis, mitral valve prolapse.

Subclinical Thyrotoxicosis

- Causes atrial fibrillation in people over age 60 years as well as bone loss in post-menopausal women.
- Serum levels of free T_4 and triiodothyronine are within the broad range of normal, but serum concentration of TSH is subnormal, often <0.1 mU/L.

Multinodular Goitre

- A toxic multinodular goitre (Plummer's disease) has at least two autonomously functioning nodules that secrete excess thyroid hormone.
- On RAIU scan, the nodule appears "hot" with increased uptake of radioactive iodine when the remainder of the thyroid gland is suppressed.

Investigations

- TSH levels are very low or undetectable. This is the primary test performed, and if normal, virtually excludes thyrotoxicosis.
- Serum T_3 and T_4 levels are elevated in the majority. T_3-thyrotoxicosis is characterised by elevated levels of T_3 and normal levels of T_4.
- Absent TSH response following intravenous TRH.
- ^{131}I uptake by the thyroid gland may be increased (not required in most patients).
- Elevated levels of antibodies to TPO.
- Measurement of TRAb may be useful in Graves' disease.
- Minor LFT abnormalities, mild hypercalcaemia and glycosuria may be present in few.

Management of Hyperthyroidism of Graves' Disease

- There are three methods of treatment:
  1. Antithyroid drugs with initial supplementation of a β-blocker.
  2. Surgical treatment.
  3. Radioactive iodine.

Antithyroid Drugs

• Carbimazole	• Propylthiouracil	• Potassium perchlorate
• Methimazole	• Lithium	• Potassium iodide

- Antithyroid drugs are often considered the primary therapy in pregnancy, in children and adolescents, and for patients who have severe Graves' eye disease.
- Potassium perchlorate reduces the uptake of iodine. Methimazole, carbimazole and thiouracil group prevent the organic binding of iodine to tyrosine in Tg by interfering with TPO. Carbimazole has an additional immunosuppressive action. Propylthiouracil also inhibits conversion of T_4 into T_3 at peripheral level and, therefore, is more useful in severe thyrotoxicosis.
- Potassium perchlorate is more toxic and induces red cell aplasia. It is used only as temporary measure in iodine-induced thyrotoxicosis (e.g. amiodarone-induced) or when no other therapy is acceptable.
- Potassium iodide is indicated only in the preparation for thyroidectomy and treatment of thyrotoxic crisis. Iodide decreases T_4 and T_3 synthesis by inhibiting iodide oxidation and organification, the Wolff–Chaikoff effect. It also blocks the release of T_4 and T_3 by inhibiting Tg proteolysis.

Carbimazole

- Given at a dose of 10–15 mg thrice daily for 3 weeks, followed by 5–10 mg thrice daily for 4–8 weeks, followed by a maintenance of 5–20 mg daily
- Maintenance dose is decided by the serum levels of T_4 and TSH, which are to be maintained in the normal range
- Total duration of treatment is usually 15–18 months
- Adverse reactions of carbimazole include rashes and blood dyscrasias, especially agranulocytosis. So, patients are instructed to stop the drug and report to the doctor in the event of a severe sore throat. Another rare side effect is hepatotoxicity

- β-blockers provide fast symptomatic improvement. Anxiety, palpitation, increased bowel activity, lid retraction and finger tremors are alleviated. The drug of choice is propranolol, given at a dose of 40–80 mg 6 hourly. β-blockers are contraindicated in cardiac failure, asthma and diabetes.

Surgical Treatment

- Subtotal thyroidectomy is the treatment of choice. Indications of surgery are:
  - Patient too young for radioactive iodine therapy (reproductive years).
  - When antithyroid drugs have failed.
  - Sensitivity reactions to antithyroid drugs.
  - Patient under 40 years with a large goitre.
- Preparation for thyroidectomy should include pre-treatment with propranolol, carbimazole and potassium iodide, 60 mg twice daily for 14 days before surgery.
- Post-operative complications of subtotal thyroidectomy are hypothyroidism, hypoparathyroidism and damage to the recurrent laryngeal nerve.

Radioactive Iodine

- Indications of radioactive iodine therapy include:
  - Patients over 40 years.
  - Young patients with a short life-span due to some other reason.
  - Young patients who are sterilised.
- Absolutely contraindicated in pregnancy and breastfeeding.
- The only complication is hypothyroidism in the ensuing years. During the lag period treat the patient with propranolol and carbimazole in severe cases.
- No evidence to suggest an increased risk of thyroid cancer and leukaemia after radioiodine therapy in adults, but data is not available for children.

Q. Describe hyperthyroid crisis, thyrotoxic crisis and thyroid crisis.

- Precipitated by severe infections in patients with previously unrecognised or inadequately treated hyperthyroidism.
- Seen shortly after thyroidectomy or ^{131}I therapy in an inadequately prepared patient.
- Seen in patients operated for some other disability without having recognised hyperthyroidism.
- Other precipitating factors include cerebrovascular accidents, acute coronary syndrome, diabetic ketoacidosis, major trauma, use of iodine contrast agents and rapid withdrawal of antithyroid medications.

Clinical Features

- This is a life-threatening increase in the severity of the clinical features of hyperthyroidism.
- Severe mental and physical exhaustion occur with delirium, delusions or mania, diarrhoea, dehydration, ketosis, tachycardia, atrial fibrillation and high-output cardiac failure. The temperature is characteristically raised.

Treatment

- Rehydration and antibiotics.
- Control hyperthermia with external cooling. DO NOT give salicylates as they cause peripheral deiodination of T_4 to T_3.
- Benzodiazepines for agitation.
- Propranolol orally or intravenously. It also blocks peripheral conversion of T_4 to T_3.
- Propylthiouracil 800–1200 mg orally followed by 200 mg every 4 hours or carbimazole 15–30 mg stat followed by 15 mg thrice daily.
- Lugol's iodine 10 drops TID about one hour after propylthiouracil or carbimazole
- Sodium ipodate (oral cholecystographic agent containing iodine) 500 mg daily.
- Lithium in a dose of 900 mg daily. It acts by inhibiting T_4 and T_3 release from thyroid and possibly by inhibiting their synthesis. Can be given in patients allergic to iodide.
- Intravenous hydrocortisone 100–200 mg every 6 hours. Glucocorticoids decrease peripheral conversion of T_4 to T_3 and treat possible relative adrenal insufficiency.
- Digoxin for cardiac failure.

Q. Describe the aetiology, clinical features, diagnosis and management of primary hypothyroidism/ Hashimoto's thyroiditis.

Q. What is myxoedema?

- The term myxoedema indicates severe hypothyroidism in which there is accumulation of hydrophilic mucopolysaccharides in the ground substance of the dermis and other tissues, leading to thickening of the facial features and doughy induration of the skin.

Classification of Hypothyroidism

- Primary hypothyroidism—due to a cause within the thyroid gland itself.
- Secondary hypothyroidism—due to failure of TSH production following pituitary or hypothalamic disease.

Common causes of Primary Hypothyroidism

• Hashimoto's thyroiditis	• Dyshormonogenesis
• Iodine deficiency (and excess)	• Drugs (PAS, lithium, amiodarone, interferon, sunitinib)
• ^{131}I therapy	• Radiation
• Thyroidectomy	

Hashimoto's Thyroiditis

- Also known as spontaneous atrophic hypothyroidism; it is the most common cause of primary hypothyroidism.
- This is an organ-specific autoimmune disorder with lymphoid infiltration of thyroid leading to fibrosis and atrophy.
- TRAb are present that block the effects of endogenous TSH.
- May be seen in some patients of Graves' disease treated with antithyroid drugs 10–20 years earlier.
- High risk of developing type 1 diabetes mellitus, pernicious anaemia and Addison's disease.

Iodine Excess

- Inhibits iodide organification and synthesis of T_4 and T_3 (Wolff–Chaikoff effect). Most people quickly escape from this effect. However, patients with abnormal thyroid glands can become hypothyroid if given iodine for more than a few days. Patients at risk for iodine-induced hypothyroidism include those with chronic autoimmune thyroiditis, partial thyroidectomy, a history of radioiodine therapy and subacute thyroiditis.

Clinical Features

• Thyroid	Enlargement of the gland
• Gastrointestinal	Decreased appetite, constipation, ileus, ascites
• Cardiorespiratory	Angina, bradycardia, hypertension, cardiac failure, pericardial effusion, pleural effusion
• Neuromuscular	Aches and pains, muscle stiffness, delayed relaxation of tendon reflexes (Woltman's sign), carpal tunnel syndrome, deafness, depression, psychosis, cerebellar ataxia, myotonia
• Dermatological	Myxoedema (non-pitting oedema of the skin of hands, feet and eyelids), dry flaky skin and hair, alopecia, vitiligo, purplish lips and malar flush, carotenaemia, erythema ab igne, xanthelasmas
• Reproductive	Menorrhagia, infertility, galactorrhoea, impotence
• Haematological	Macrocytosis, anaemia
• Miscellaneous	Tiredness, somnolence, cold intolerance, hoarseness of voice, low-pitched voice, slurred speech, weight gain

- Other causes of delayed relaxation of tendon reflexes include anorexia nervosa, advanced age, peripheral oedema, hypothermia, peripheral arterial disease and pregnancy.
- Myxoedema facies is a peculiar facial appearance due to periorbital puffiness resulting from myxoedema, scanty eyebrows, facial pallor due to vasoconstriction and anaemia, a lemon-yellow tint of the skin due to carotenaemia (caused by reduced conversion of carotene to vitamin A), purplish lips and malar flush.
- Subclinical hypothyroidism is a milder degree of thyroid failure characterised by mild to moderate increase in serum TSH but with T_4 values still within normal range. Antithyroid antibodies can be detected in 80% of these patients. Progression from subclinical to overt hypothyroidism occurs in 5–18% of persons with subclinical hypothyroidism per year. Levothyroxine therapy should be started if TSH > 10.0 mIU/L while therapy needs to be individualised if TSH < 10.0 mIU/L.

Investigations

- Serum T_4 levels are low and TSH levels are high.
- Serum cholesterol and triglyceride (TG) levels are raised.

- Serum lactate dehydrogenase (LDH) and creatine kinase (CK) levels are raised.
- Serum sodium levels may be low.
- Electrocardiogram demonstrates sinus bradycardia, low voltage QRS complexes and ST–T wave abnormalities.
- Chest radiograph may show enlarged cardiac shadow.

Treatment

- Hypothyroidism is treated with T_4. It is usually given at a dose of 50 µg/day for 3 weeks, followed by 100 µg/day for 3 weeks, followed by a maintenance dose of 150 µg/day. The correct dose of T_4 is that which restores serum TSH to below 3 mU/L. It should be given on empty stomach in the morning.
- In elderly patients and those with ischaemic heart disease T_4 is started at a lower dose of 25 µg/day.
- In a few patients with ischaemic heart disease angina may develop or worsen with T_4 therapy. They should be treated with β-blockers and vasodilators, or CABG, or balloon angioplasty. This allows full replacement dosage of T_4.

Q. Describe myxoedema coma and myxoedema madness.

- This is a rare complication of hypothyroidism, seen usually in elderly patients.
- More than 90% of cases occur during the winter months.
- The usual precipitating causes are infections, drugs (amiodarone, anaesthetic agents, barbiturates, β-blockers, diuretics, lithium, narcotics, phenothiazines), cardiac failure, hyponatraemia, hypoxia and hypercapnia.
- Patients with myxoedema coma usually have long-standing hypothyroidism; although it may not have been previously diagnosed.
- The patient presents with hypothermia and neuropsychiatric manifestations. They develop psychosis with delusions and hallucinations ("myxoedema madness"), progressing to depressed level of consciousness, convulsions and coma ("myxoedema coma").
- Metabolic abnormalities include hyponatraemia and hypoglycaemia.
- Arterial blood gases often reveal respiratory acidosis, hypoxia and hypercapnia.
- The cerebrospinal fluid pressure is low and protein content may be elevated.

Management

- Treatment of precipitating cause.
- Any patient with suspected myxoedema coma should be treated presumptively with thyroid hormone. As T_3 is more biologically active than T_4 most physicians recommend intravenous T_3 (20 µg 8 hourly). However, parenteral T_3 is not easily available. Therefore, intravenous T_4, initially 100–150 µg and then 75–100 µg daily, is recommended. If intravenous formulation is not available, T_4 may be administered orally in a dose of 300 µg stat followed by 100–300 µg daily.
- Hydrocortisone sodium succinate 100 mg intravenously 8 hourly.
- Correction of hyponatraemia and hypoglycaemia.
- Supportive therapy includes gentle warming of the patient with blankets, intravenous fluids, broad-spectrum antibiotics, high-flow oxygen and rarely assisted ventilation.

Q. Briefly outline the neuropsychiatric manifestations of hypothyroidism.

• Muscle aches, pains and stiffness	• Hypothermia
• Carpal tunnel syndrome	• Cerebellar ataxia
• Myxoedema madness	• Cerebral cortical degeneration
• Myxoedema coma	• Deafness
• Delayed relaxation of DTR	• Myotonia
• Mental retardation (in cretinism)	• Depression, psychosis

Q. Give a brief account of sick euthyroid syndrome.

- Also known as non-thyroidal illness syndrome; it refers to abnormal findings on thyroid function tests in patients with severe illnesses not caused by primary thyroid or pituitary dysfunction.
- Conditions associated with euthyroid sick syndrome include malnutrition, anorexia nervosa, trauma, myocardial infarction, chronic renal failure, diabetic ketoacidosis, cirrhosis and sepsis.

- Most common pattern of abnormality is low levels of total T_3, with normal T_4 and TSH (low T_3 syndrome). Peripheral conversion of T_4 to T_3 is reduced, leading to increase in reverse T_3 (rT_3). There is reduced clearance of rT_3 in these patients that is the major cause of raised rT_3. In true hypothyroidism, rT_3 will be low.
- In severe illness, T_4 may also fall (low T_4 syndrome). This indicates a poor prognosis. This is partly related to altered binding to TBG. Therefore, free T_4 is normal. TSH levels fluctuate from low to high.
- TSH concentration is usually low but detectable in seriously ill patients.
- No role for levothyroxine treatment in sick euthyroid syndrome.

Q. What are the causes of thyroiditis?

- The term thyroiditis encompasses a heterogeneous group of disorders characterised by thyroid inflammation.

Causes of Thyroiditis

• Acute	Bacterial infections (e.g. staphylococcal, streptococcal), fungal infections (*Aspergillus, Candida, Histoplasma*), radiation (e.g. thyroiditis after radioiodine treatment), amiodarone
• Subacute	Viral or granulomatous (de Quervain's thyroiditis), mycobacterial infection, post-partum thyroiditis
• Chronic	Autoimmune (Hashimoto's thyroiditis, Graves' disease), Reidel's thyroiditis, parasitic infections

Q. Describe subacute thyroiditis (de Quervain's thyroiditis).

- Virus-induced (Coxsackie, mumps, adenovirus) inflammation of thyroid gland results in release of colloid and its contents into the bloodstream.
- Characterized by systemic symptoms and pain in the region of thyroid gland radiating to the angle of the jaw and ears. Pain is made worse by swallowing, coughing and movement of the neck.
- The thyroid gland is enlarged and tender. ESR is usually raised.
- Thyroid radionuclide uptake is reduced or absent.
- Serum Tg is raised in most patients.
- Initially there is hyperthyroidism (with elevated T_3 and T_4 and depressed TSH), which is followed by a period of hypothyroidism, and finally full recovery in 4–6 months. In less than 5% cases, hypothyroidism may persist.
- Treated with aspirin or other non-steroidal anti-inflammatory drugs, prednisolone (in severe disease) and propranolol.
- Therapy for hyperthyroidism is not often needed because symptoms are mild and short-lived.

Q. What is Hashimoto's thyroiditis? Discuss briefly its investigations and treatment.

Q. Give a brief account of chronic autoimmune thyroiditis.

- It is an autoimmune condition characterised by high titres of circulating antibodies to TPO and Tg.
- It is the commonest cause of goitrous hypothyroidism.
- Common in middle-aged females, and is often associated with ulcerative colitis or type 1 diabetes mellitus.
- Pathologically there is lymphocytic infiltration, fibrosis and follicular cell hyperplasia of thyroid.
- Most patients are asymptomatic, though some may complain of a feeling of tightness or fullness in the neck; however, neck pain and tenderness are rare.
- Diffuse enlargement of thyroid with a characteristic firm or rubbery consistency.
- Twenty-five percent of them present with hypothyroidism, the rest are at a higher risk of developing it later.

Investigations

- Thyroid function tests suggest hypothyroidism.
- Serum contains antibodies to TPO and Tg.
- Antinuclear antibodies (ANA) may be positive in the young.
- Ultrasound of thyroid shows reduced echogenicity.
- Fine-needle aspiration cytology from a thyroid nodule.

Treatment

- Thyroxine (150–200 μg/day) is effective in hypothyroidism, and can also bring about goitre shrinkage.

Q. Briefly outline the clinical features, investigations and treatment of endemic goitre.

Q. What is Jod–Basedow phenomenon?

- When iodine deficiency manifests as diffuse goitre in a particular geographic region, where more than 5% of the population is affected, it is called endemic goitre.
- These endemic belts are characterized by:
  - A daily iodine intake of less than 50 μg (normal recommendation is 100 μg/day in children).
  - Very low iodine content in drinking water.
  - Deficient dietary sources of iodine like sea-fish, milk and eggs.
- Occasionally, goitre may be due to ingestion of goitrogens (e.g. cassava roots, cabbage, cauliflower).
- In India, it is estimated that more than 6.1 crore people are suffering from endemic goitre and 88 lakh people are mental/motor handicaps due to it.
- Goitre is one of the several disorders that occur due to iodine deficiency. All the disorders are categorised under a term "iodine deficiency disorders" (IDD).

Clinical Features

- Endemic goitre manifests clinically as a diffuse enlargement of the thyroid with a patient in euthyroid state in the initial stage. This is known as simple goitre. Later, hypothyroidism develops.
- In children and adults endemic goitre may be associated with features of hypothyroidism and mental retardation.
- Cretinism: Iodine deficiency during pregnancy causes severe hormone-induced physiological damage to foetus and newborn resulting in cretinism (stunting, deaf-mutism, malformed limbs, spastic motor disorders, goitre, as well as mental impairment).
- The goitre is initially diffuse but eventually becomes nodular because the cells in some thyroid follicles proliferate more than others.

Investigations

- Plasma inorganic iodide levels are low.
- Urinary iodide excretion is low (<50 μg/day).
- Serum T_4 is normal; T_3 may be normal or elevated (due to enhanced conversion of T_4 to T_3).
- TSH may be normal or mildly elevated suggesting increased sensitivity to TSH.

Treatment

- Iodine replacement in early cases.
- Suppressive therapy with T_4.

Preventive Measures

- Fortification of common salt with iodine.
- Intramuscular injection of 3–4 mL of iodized oil once in 2 years.
- "Jod–Basedow phenomenon" is the development of acute hyperthyroidism following iodine replacement. It is due to enhanced thyroid hormone production by autonomous nodules that may be present in some cases.

Q. Classify hyperparathyroidism.

Q. Discuss the clinical features, investigations and management of primary hyperparathyroidism.

Classification and causes	
• Primary	Autonomous secretion of PTH by parathyroid. Serum calcium and PTH are raised. Causes— single adenoma (90%), multiple adenomata, nodular hyperplasia and carcinoma; rarely lithium and thiazides
• Secondary	Parathyroid hyperplasia with increased PTH secretion in an attempt to compensate for prolonged hypocalcaemia. Serum calcium is low and PTH is raised. Causes—chronic renal failure, malabsorption, osteomalacia and rickets
• Tertiary	Adenoma formation and autonomous PTH secretion occurring in cases of secondary hyperparathyroidism. Serum calcium and PTH are raised

Clinical Features

- More than 70% are diagnosed by incidental finding of hypercalcaemia.
- Non-specific symptoms.
  - Anorexia, nausea, vomiting, constipation and weight loss.
  - Weakness, lassitude and tiredness.
  - Drowsiness, poor concentration, memory loss and depression.
- Renal manifestations.
  - Polyuria and polydipsia.
  - Recurrent calculus formation.
  - Nephrocalcinosis---deposition of calcium salts in the renal parenchyma.
  - Impairment of renal function with uraemia, hypokalaemia, hyperuricaemia, hyperchloraemic acidosis and dilute urine.
- Skeletal manifestations.
  - Bone pain, osteopenia, osteoporosis, fractures and deformity due to osteitis fibrosa cystica.
  - Localised bone swelling, especially of the mandible.
  - Degenerative arthritis and attacks of acute pseudogout, especially of the knee joints due to chondrocalcinosis affecting the menisci.
- Other manifestations.
  - Corneal calcification, best seen by slit-lamp examination.
  - Calcification of arterial walls and soft tissues of hand.
  - Peptic ulceration.
  - Hypertension.
  - Myopathy.
- Primary hyperparathyroidism, secondary to a parathyroid adenoma, may be a part of multiple endocrine neoplasia syndrome.
  - MEN 1 (Werner's syndrome) consists of tumours of the pituitary, pancreas and parathyroid glands. Other abnormalities often seen include Zollinger–Ellison syndrome.
  - MEN 2A is characterised by phaeochromocytoma and medullary carcinoma of thyroid as well as hyperparathyroidism.
  - MEN 2B has additional multiple neuromas but hyperparathyroidism is not present.

Investigations

- Biochemical abnormalities.
  - Raised serum calcium and raised intact PTH. Serum calcium concentrations should be corrected to the prevailing serum albumin concentration. The total calcium level can be corrected for low albumin levels by adding 0.8 mg/dL to the total serum calcium level for every 1.0 g/dL by which the serum albumin concentration is lower than 4 g/dL.
    - Vitamin D levels should be checked initially because presence of vitamin D deficiency can affect the interpretation of the PTH assay resulting in elevated PTH levels.
  - Serum phosphate is usually low.
  - Raised serum chloride.
  - Serum alkaline phosphatase may be raised depending on the degree of bone involvement.
- Urine.
  - Hypercalciuria (>300 mg/24 hours) in 30% cases.
  - Increased markers of bone resorption (urinary pyridinoline, deoxypyridinoline and N-telopeptide of collagen).
- ECG.
  - Shortened QT interval.
  - Cardiac arrhythmias (rare).
- Radiological abnormalities.
  - Demineralization and subperiosteal erosions of phalanges, most marked on the radial side of the middle phalanx.
  - Resorption of the terminal phalanges.
  - "Pepper–pot" appearance of the skull on the lateral view.
  - Nephrocalcinosis—scattered opacities within the renal outline.
  - Soft tissue calcification (e.g. arterial wall).
- Dual-energy X-ray absorptiometry (DEXA) and CT scan show reduced bone density.
- Investigations for localisation of the tumour.
  - High-resolution ultrasonography.
  - Selective neck vein catheterisation with PTH measurements.
  - CT scanning and subtraction imaging.
  - Scintigraphy with technetium-99 sestamibi.

Treatment

- Treatment of hypercalcaemia (see below).
- Adenoma is treated by surgical removal.
- Hyperplasia is treated by removal of all four glands and transplantation of some of the excised tissue to the forearm.

Q. Discuss the clinical presentation and management of hypercalcaemic crisis.

- Seen in elderly patients with primary hyperparathyroidism.
- Clinical features include dehydration, hypotension, abdominal pain, vomiting, pyrexia and altered conscious level.
- ECG may show AV block, prolonged PR and QRS, bundle branch blocks and shortened QT interval.
- The definitive treatment is surgical if it is due to hyperparathyroidism.
- Medical management includes correction of dehydration, electrolyte imbalance and hypercalcaemia.
- Dehydration is corrected with 4–6 L of 0.9% saline intravenously over 24 hours followed by diuretics.
- Electrolyte imbalances like hypokalaemia and hypomagnesaemia are corrected by intravenous supplementation.
- Hypercalcaemia usually gets corrected by intravenous fluids, but rarely requires other measures.
  - Salmon calcitonin 200–400 IU subcutaneously 8 hourly.
  - Mithramycin 25 µg/kg intravenously over 6 hours/day.
  - Neutral phosphate (0.1 M) 500 mL intravenously over 6–8 hours.
  - Corticosteroids and bisphosphonates (see under hypercalcaemia).

Q. What are the causes of hypercalcaemia? Outline the management of hypercalcaemia.

Q. Describe salmon calcitonin.

- Parathyroid hormone (PTH), 1, 25-dihydroxyvitamin D_3 (calcitriol) and calcitonin control calcium homeostasis in the body.
- Normal serum calcium levels are 8–10 mg/dL (2.0–2.5 mmol/L).
- Normal ionized calcium levels are 4–5.6 mg/dL (1–1.4 mmol/L).
- Hypercalcaemia is considered mild if the total serum calcium level is between 10.5 and 12 mg/dL (2.6–3 mmol/L) while levels above 14 mg/dL indicate severe hypercalcaemia.

Causes

Parathyroid hormone related	Vitamin D related
- Primary hyperparathyroidism	- Vitamin D intoxication
- Lithium therapy	- Granulomatous diseases (sarcoidosis, tuberculosis,
- Familial hypocalciuric hypercalcaemia	berylliosis)
	- Idiopathic hypercalcaemia of infancy
Malignancy related	**High bone turnover**
- Humoral-mediated (e.g. PTH-related peptide)	- Immobilization
- Tumours of lung and kidney	- Hyperthyroidism
- Local osteolysis-mediated	- Thiazide diuretics
- Breast carcinoma	
- Multiple myeloma	**Associated with renal failure**
	- Secondary hyperparathyroidism
	- Aluminium intoxication
	- Milk–alkali syndrome

- Lithium decreases parathyroid gland sensitivity to calcium.
- Familial hypocalciuric hypercalcaemia is due to a mutation in calcium-sensing receptor in parathyroid glands and kidneys

Clinical Features

- Discussed under "hyperparathyroidism".

Management

Generally Useful Measures

- In mild hypercalcaemia (<12 mg/dL), simple oral hydration along with increased salt intake is sufficient. Many hypercalcaemic patients are dehydrated because of poor intake, vomiting, confusion or hypercalcaemia-related defects in renal concentrating ability.
- Diuretics like furosemide 40–160 mg/day or ethacrynic acid 50–200 mg/day (after correction of volume).

- Forced diuresis with 4–6 L of intravenous fluid/day and furosemide 2 hourly. Sodium, potassium and magnesium should be supplemented. Saline acts by decreasing concomitant reabsorption of sodium and calcium in both the proximal and distal renal tubules, and enhancing urinary calcium excretion by increasing glomerular filtration rate.
- Prednisolone 5–15 mg 6 hourly orally or hydrocortisone 50–100 mg IV 6 hourly. Steroids inhibit vitamin D conversion to calcitriol and are useful in vitamin D intoxication, haematologic malignancies and granulomatous diseases.
- Oral phosphate 250 mg 6 hourly.
- Mithramycin 10–25 µg/kg intravenously over 6 hours for 3–8 days.

Special Therapies in Selected Cases

- Neutral phosphate (0.1 M) 500 mL intravenously over 6–8 hours.
- Intravenous bisphosphonates (pamidronate, zoledronic acid, ibandronate) are useful in malignancy-associated hypercalcaemia. These agents inhibit osteoclast action, thereby reducing bone resorption. Most commonly used agent is pamidronate in a dose of 60–90 mg intravenously over 4 hours. Effect of bisphosphonates on serum calcium concentrations is apparent after 24–48 hours.
- Salmon calcitonin 200–400 IU subcutaneously 8 hourly for 24 hours. It inhibits bone resorption and augments renal excretion of Ca++. It is used in severe hypercalcaemia refractory to other measures.
- Indomethacin 25 mg 6 hourly orally in some cases with malignancy-induced hypercalcaemia.
- Haemodialysis with a low-calcium bath.

Q. Give a brief account of the causes and general management of hypoparathyroidism.

- The common clinical manifestation is tetany, irrespective of the cause (see under "hypocalcaemia" below).
- Characteristically serum calcium is low, serum phosphate is high and PTH is low or inappropriately normal.

Causes

- Post-operative hypoparathyroidism.
- Infantile hypoparathyroidism.
- Idiopathic hypoparathyroidism
- DiGeorge syndrome (asymptomatic hypocalcaemia due to hypoparathyroidism, thymic hypoplasia with immunodeficiency, congenital heart defects)
- Autoimmune polyendocrinopathy type 1 (chronic mucocutaneous candidiasis, hypoparathyroidism and autoimmune adrenal failure).
- Pseudohypoparathyroidism (resistance to PTH; PTH is high).

Treatment

- In the acute phase, calcium is given intravenously as for tetany.
- Substitution therapy is provided by 1-α-hydroxycholecalciferol (alphacalcidol) or 1, 25 dihydroxycholecalciferol (calcitriol), both at a dose of 0.25–2 µg/day.
- In the long-term, thiazide diuretics are useful as they enhance renal calcium reabsorption and increase serum calcium.

Q. What are the causes of tetany? Give the clinical picture and management of tetany.

Q. Explain briefly Trousseau's sign and Chvostek sign.

Causes

- Tetany is caused by an increased excitability of peripheral nerves due to hypocalcaemia or alkalosis or hypomagnesaemia.

Due to hypocalcaemia	Due to alkalosis
- Malabsorption	- Repeated vomiting of gastric juice
- Hypoparathyroidism	- Excessive intake of oral alkalis
- Osteomalacia (vitamin D deficiency)	- Hyperventilation—e.g. hysteria
- Acute pancreatitis	- Primary hyperaldosteronism
- Chronic renal failure	**Due to hypomagnesaemia**

Clinical Features

- In children the characteristic triad of carpopedal spasm, stridor and convulsions occur. In "carpal spasm" the metacarpophalangeal joints are flexed, the interphalangeal joints are extended and there is opposition of the thumb (main d'accoucheur).
- In adults there is tingling in the hands, feet and around the mouth (circumoral paraesthesia).
- Latent tetany may be present when signs of overt tetany are lacking. It is recognised by eliciting two signs:
  - Trousseau's sign—Inflation of sphygmomanometer cuff on the upper arm to more than systolic pressure is followed by the characteristic carpal spasm within 3 minutes.
  - Chvostek sign—Tapping over the branches of facial nerve as they emerge from the parotid gland produces twitching of the facial muscles.

Treatment

Control of Tetany

- Slow intravenous injection of 20 mL of 10% solution of calcium gluconate is rapidly effective.
- If tetany is not relieved administration of magnesium may be required.

Correction of Alkalosis

- Persistent vomiting is treated with intravenous isotonic saline and potassium.
- In alkali excess, its withdrawal and if necessary, ammonium chloride 2 g 4 hourly orally will control tetany.
- Hysterical hyperventilation may be controlled by re-breathing expired air from a suitable bag or inhalation of 5% carbon dioxide in oxygen.

Q. Mention the hormones secreted by the adrenal gland.

- Adrenal gland has an inner medulla and an outer cortex. The adrenal cortex is divided into three zones: zona glomerulosa, zona fasciculata and zona reticularis.

Site	Class	Hormone
• Adrenal cortex		
• Zona glomerulosa	Mineralocorticoid	Aldosterone
• Zona fasciculate	Glucocorticoid	Cortisol
• Zona reticularis	Androgens	Dehydroepiandrosterone sulphate, dehydroepiandrosterone, androstenedione
• Adrenal medulla	Catecholamines	Adrenaline, noradrenaline

Q. Discuss the causes, clinical features, investigations and management of Cushing's syndrome.

Q. Write a short note on Cushing's disease.

- Cushing's syndrome is defined as the symptoms and signs associated with corticosteroid excess of long duration.
- Cushing's disease is corticosteroid excess due to pituitary-dependent bilateral adrenal hyperplasia. The pituitary tumours in Cushing's disease are usually microadenomas (<10 mm in size) that generally do not cause symptoms by local mass effect. Macroadenomas are uncommon in these patients. These tumours generally retain some negative feedback responsiveness to high doses of glucocorticoids. It is usually sporadic but may be associated with multiple endocrine neoplasia type 1.

Causes of Cushing's Syndrome

ACTH dependent	ACTH independent
• Cushing's disease	• Iatrogenic (use of corticosteroids)
• Ectopic ACTH syndrome (tumours)	• Adrenal adenoma
• Iatrogenic (ACTH therapy)	• Adrenal carcinoma
• Ectopic corticotrophin-releasing hormone syndrome (rare)	• Micronodular hyperplasia (rare)
• Macronodular hyperplasia (initial stages)	• Macronodular hyperplasia (rare)

- Cushing's syndrome of pituitary origin (Cushing's disease) is more common in females.
- Ectopic ACTH syndrome, usually due to small cell carcinoma of lung, is more common in males. Other tumours include carcinoid of thymus, pancreatic carcinoma and bronchial adenoma. Ectopic sources of ACTH are generally not responsive to negative feedback with high doses of glucocorticoids.
- Excluding iatrogenic group, pituitary-dependent Cushing's disease is the most common cause of Cushing's syndrome (80%).

Clinical Features

Symptom	Cause
- Weight gain	Accumulation of fat and fluid retention
- Hirsutism	Increased adrenal androgen secretion
- Back pain	Osteoporosis and vertebral compression fractures
- Muscle weakness	Proximal myopathy and hypokalaemia
- Oligomenorrhoea, amenorrhoea and impotence	Gonadal dysfunction
- Depression, irritability, psychosis	

Sign	Cause/description
- Central obesity ("lemon on match-stick")	Centripetal distribution of fat
- Buffalo hump	Fat accumulation at the lower part of neck
- Plethoric appearance	Thinning of the skin
- Moon face	Rounded plethoric appearance
- Bruising	Thinning of blood vessels from collagen breakdown
- Purplish striae over abdomen, buttocks and thighs	Thinning of the skin from collagen breakdown
- Hypertension	Increase in plasma volume and sodium retention
- Proximal myopathy	Loss of protein in muscle
- Skin infections	Tinea versicolor

- Systemic fungal infections may occur in untreated patients.
- Risk of coronary artery disease and venous thrombosis higher than general population
- Impaired glucose tolerance due to increased gluconeogenesis, stimulation of lipolysis and proteolysis, and potentiation of glucagon effect
- Hypercoagulability

Features of Cushing's Syndrome Due to Ectopic ACTH Secretion

- Hypokalaemic alkalosis.
- Skin pigmentation.

Investigations in Cushing's Syndrome

Hormonal Studies

- Hormonal studies are done in a stepwise manner. Studies are aimed at the diagnosis of Cushing's syndrome and establishing its cause.

Tests Establishing the Presence of Cushing's Syndrome

- Plasma cortisol levels—In normals, measurement of plasma cortisol levels at 8 am and 12 midnight will show the lowest levels at 12 midnight. In Cushing's syndrome this circadian rhythm is lost and the cortisol levels remain the same throughout the day. A midnight level below 1.8 μg/dL is normal, and has a high sensitivity for excluding Cushing's syndrome. However, specificity is low.
- 24-hour urinary cortisol excretion is raised in Cushing's syndrome (normal value <90 μg/24 hours). Milder elevations of urinary cortisol can be found in conditions such as chronic anxiety, depression, polycystic ovary and alcoholism, all of which are also known as pseudo-Cushing states.
- Overnight dexamethasone suppression test—The patient takes 1 mg dexamethasone at 11 pm and the plasma cortisol is measured at 8 am the following day. Normal value is less than 1.8 μg/dL (previous value was <5 μg/dL but reduction to 1.8 μg/dL has increased the sensitivity of the test). In Cushing's syndrome cortisol levels are not suppressed. The test may be falsely positive in alcoholics or obese patients.

- Low-dose dexamethasone suppression test—It is not routinely performed. If urinary-free cortisol or overnight dexamethasone suppression tests are borderline, then this test is performed. The patient is administered 0.5 mg dexamethasone 6 hourly for 2 days. 24-hour urine is collected from second day and plasma is collected for cortisol on third day. If the urinary-free cortisol falls below 10 μg/24 hours or plasma cortisol is below 1.8 μg/dL, it excludes the diagnosis of Cushing's syndrome.

Conditions Causing an Apparent Lack of Cortisol Suppression

• Reduced dexamethasone absorption • Drugs enhancing hepatic dexamethasone metabolism (barbiturates, phenytoin, carbamazepine, rifampicin, meprobamate, aminoglutethimide, methaqualone)	• Increased concentration of cortisol binding globulin (oestrogen treatment, pregnancy) • Pseudo-Cushing states (anxiety, obesity, alcoholic)

- Late-night salivary cortisol—This appears to be promising for the screening of Cushing's syndrome. Cortisol concentration in saliva is highly correlated with free plasma cortisol, independent of salivary flow rates and stable at room temperature for 1 week.

Tests Establishing the Cause of Cushing's Syndrome

- Plasma ACTH level at 8 am
  - Very high levels (>300 ng/L) suggest ectopic ACTH syndrome.
  - Normal levels (10–80 ng/L) suggest a pituitary source.
  - Intermediate values (80–300 ng/L) suggest either pituitary-dependent disease or ectopic ACTH syndrome.
  - Low ACTH (<10 ng/L) suggests adrenal tumours, macronodular adrenal hyperplasia or exogenous steroid administration.
- High-dose dexamethasone suppression test.
  - In this test, 2 mg dexamethasone is administered 6 hourly for 2 days. 24-hour urine is collected from 2nd day and plasma is collected for cortisol on 3rd day. If the urinary-free cortisol falls below 10 μg/24 hours or plasma cortisol is below 1.8 μg/dL, it indicates suppression of axis and is considered a positive test. This test is positive in pituitary-dependent disease. It is negative in ectopic ACTH syndrome and adrenal tumours.
- Plasma potassium levels.
  - Normal in pituitary-dependent disease and adrenal tumours.
  - Low (<3.5 mmol/L) in ectopic ACTH syndrome.
- ACTH/cortisol response to corticotrophin-releasing factor (CRF).
  - Increased levels in pituitary-dependent disease.
  - Unchanged levels in ectopic ACTH syndrome and adrenal tumours.
- Bilateral inferior petrosal sinus sampling for ACTH before and after CRF stimulation.

Other Investigations

- Blood sugar, cholesterol and LDL may be elevated. Frank diabetes may occur in 25–50% of patients
- Plain radiograph of the skull.
- CT/MRI head.
- Radiograph of chest to detect bronchogenic carcinoma.
- CT scan of anterior mediastinum and upper abdomen including pancreas to rule out tumours.
- MRI abdomen.

Management

Adrenal Tumours

- Metyrapone or aminoglutethimide can reduce cortisol overproduction by blocking its production.
- Adrenal adenomas are removed surgically. Replacement therapy with prednisolone is given post-operatively till the contralateral adrenal, hypothalamus and pituitary recover.
- Adrenal carcinomas are resected surgically. The tumour bed is irradiated and the patient is given the adrenolytic drug, *o,p*'DDD (mitotane).

Cushing's Disease

- Metyrapone or ketoconazole may be given during the preparation for surgery to reduce the clinical effects of hypercortisolism.
- Trans-sphenoidal surgical removal of the adenoma is the treatment of choice.
- If no tumour is found, radical hypophysectomy is done.

- Radiotherapy and radiosurgery for the treatment of recurrent or residual ACTH-secreting tumours.
- If the diagnosis is uncertain, bilateral adrenalectomy is done. This should be followed by pituitary irradiation to prevent the development of Nelson's syndrome.
- Following successful adrenalectomy, prednisolone and fludrocortisone should be given post-operatively for a variable length of time.

Ectopic ACTH Syndrome

- Benign tumours like bronchial carcinoid should be removed.
- Malignant tumours are treated with radiotherapy and chemotherapy.
- Recurrence may be treated with metyrapone or aminoglutethimide.

Q. What is Nelson's syndrome?

- Develops in patients with Cushing's disease (pituitary-dependent bilateral adrenal hyperplasia) treated by bilateral adrenalectomy with no definitive treatment for pituitary.
- Characterized by an aggressive locally invasive pituitary tumour with very high levels of ACTH in the blood and hyper-pigmentation of skin.
- Treatment includes surgery and radiotherapy.

Q. Discuss the aetiology, clinical features, diagnosis and management of primary hyperaldosteronism.

Q. Describe Conn's syndrome.

- Overproduction of the hormone aldosterone is called hyperaldosteronism.
- Primary hyperaldosteronism is due to an abnormality in the zona glomerulosa of the adrenal gland.
- Secondary hyperaldosteronism results from the stimulation of aldosterone secretion by angiotensin II following activation of renin–angiotensin system.

Primary Hyperaldosteronism

Aetiology

- Adenoma (Conn's syndrome).
- Bilateral zona glomerulosa hyperplasia.
  - Idiopathic.
  - ACTH dependent (glucocorticoid-responsive or dexamethasone-suppressible). In this type of hyperaldosteronism the secretion of aldosterone is under ACTH control. Therefore, treatment is by administering glucocorticoids that suppresses ACTH release.

Pathophysiology

- Excess aldosterone produces sodium retention, potassium loss and metabolic alkalosis.

Clinical Features

- Hypertension and hypokalaemia.
- Muscle weakness from hypokalaemia.
- Tetany due to metabolic alkalosis.
- Polyuria and polydipsia due to nephrogenic DI induced by hypokalaemia.

Investigations

Diagnosis

- Hypokalaemia; elevated urinary potassium (>30 mEq/day during hypokalaemia is inappropriate).
- Plasma aldosterone concentration (PAC) is elevated (>15 ng/dL).
- Plasma renin activity (PRA) is suppressed.
- PAC:PRA ratio is the accepted screening test for primary hyperaldosteronism. A level above 20 is considered abnormal when plasma aldosterone is measured in ng/dL and PRA is measured in ng/mL/hour.
- Other tests include oral salt loading test, saline infusion test and captopril test.
  - Suppression of aldosterone below 8.5 ng/dL with salt loading rules out primary hyperaldosteronism.
  - Oral captopril does not produce any significant decrease in PAC in primary hyperaldosteronism.

Differential Diagnosis

- CT/MRI scanning can detect adenoma and hyperplasia.
- Adrenal vein catheterization.
  - Unilateral hypersecretion of aldosterone is seen in adenoma.
  - Bilateral hypersecretion of aldosterone is seen in hyperplasia.
- Dexamethasone.
  - Lowers plasma aldosterone transiently in adenoma.
  - Prolonged suppression in glucocorticoid-sensitive hyperaldosteronism.
- Measurement of 18-OH-cortisol levels.
  - Very high in adenomas and glucocorticoid-responsive hyperplasia.
  - Slight elevation in idiopathic hyperplasia.
- Scanning of the adrenal with selenium-75-cholesterol can detect an adenoma.

Management

- The aldosterone antagonists, spironolactone and eplerenone, are effective in patients where surgery cannot be done. Spironolactone may require high doses (up to 400 mg/day). A few patients develop gynaecomastia with spironolactone; the incidence is lower with eplerenone. Another option is to give amiloride (10–40 mg/day).
- Unilateral adrenalectomy may be done in an adenoma.
- Angiotensin-receptor blockers may be given for control of hypertension. These agents also reduce the ill-effects of excessive aldosterone on various tissues. ACE inhibitors may also be given to control blood pressure.

Q. Give a brief account of secondary hyperaldosteronism.

- Secondary hyperaldosteronism results from aldosterone excess mediated through the renin–angiotensin system.

Conditions Causing Secondary Hyperaldosteronism

- Physiological	Salt depletion from inadequate intake or excessive loss through kidney or gastrointestinal tract; pregnancy
- Pathological	Excessive diuretic therapy, nephrotic syndrome, cirrhosis with ascites, congestive heart failure, Bartter's syndrome, accelerated or malignant phase of hypertension, severe renal artery stenosis

Investigations

- Hypokalaemia.
- Plasma aldosterone levels are elevated.
- PRA is elevated.

Management

- Salt depletion is treated with intravenous saline.
- Congestive heart failure is treated with spironolactone and ACE inhibitors.
- Bartter's syndrome is treated with spironolactone and indomethacin.
- Accelerated or malignant hypertension is treated with antihypertensive drugs.
- Renovascular disease is treated with ACE inhibitors, but definitive therapy is angioplasty or surgical correction.
- If excessive diuretic therapy (e.g. thiazide) is the cause, it should be substituted or supplemented with one of the potassium-sparing diuretics like spironolactone, amiloride or triamterene.

Q. How do you classify adrenocortical insufficiency?

Q. Write a short note on Addison's disease.

Classification and Causes

Primary causes (adrenal causes)	Secondary causes (inadequate ACTH)
- Addison's disease	- Hypothalamic or pituitary diseases
- Congenital or acquired enzyme defects	- Withdrawal of glucocorticoid therapy

Addison's Disease

- Indicates adrenocortical insufficiency due to destruction or dysfunction of entire adrenal cortex.

Causes

• **Autoimmune adrenalitis**
• **Infectious adrenalitis**
  • Tuberculosis
  • Fungal (histoplasmosis)
• **Adrenal haemorrhage**
  • Waterhouse–Friderichsen syndrome
  • Anticoagulation therapy
  • Trauma (external or by invasive procedures)
• **Adrenal infarction (due to thrombosis)**
  • Systemic lupus erythematosus
  • Polyarteritis nodosa
  • Antiphospholipid syndrome
• Trauma
	• **Metastases in the adrenal**
	  • Lung, breast, stomach carcinomas
	  • Lymphoma
	• **Drug induced**
	  • Adrenolytic therapy (e.g. mitotane)
	  • Other agents (ketoconazole, etomidate, rifampin, cyproterone acetate)
	• **Genetic**
	  • Congenital adrenal hyperplasia
	• **Others**
	  • Bilateral adrenalectomy
	  • Amyloidosis
	  • Haemochromatosis
	  • Sarcoidosis

Clinical Features

- Clinical features of Addison's disease result from glucocorticoid deficiency, mineralocorticoid deficiency, androgen deficiency and ACTH excess.
- The cardinal features of Addison's disease are hypotension, pigmentation and previous history of acute adrenal crisis following stress, or slow recovery from illness.
- Glucocorticoid deficiency results in malaise, weakness, weight loss, anorexia, nausea, vomiting, diarrhoea or constipation, postural hypotension and hypoglycaemia.
- Mineralocorticoid deficiency manifests as hypotension. Many patients have salt craving.
- ACTH excess results in pigmentation of exposed areas, pressure areas like elbows, knees and knuckles, palmar creases, mucous membranes, conjunctivae and recently acquired scars. Other areas where pigmentation can occur include perineum, axillae and areolae of breasts. It occurs due to increased production of pro-opiomelanocortin, a prohormone that is cleaved into biologically active hormones ACTH and melanocyte-stimulating hormone.
- Androgen deficiency results in diminution of body hair, especially in females, and usually occurs with a secondary cause of adrenal insufficiency.
- A number of autoimmune diseases may be associated with Addison's disease. They include Hashimoto's thyroiditis, primary atrophic hypothyroidism, pernicious anaemia, type 1 diabetes mellitus, primary ovarian failure and hypoparathyroidism.
  - The association of two or more of these endocrinopathies is known as type II polyglandular autoimmune syndrome.
  - The combination of adrenal insufficiency, hypoparathyroidism and chronic mucocutaneous candidiasis constitutes type I polyglandular autoimmune syndrome.
  - The association of Addison's disease and Hashimoto's thyroiditis is known as Schmidt syndrome.

Investigations

- Elevated blood urea, hyponatraemia and hyperkalaemia.
- Low blood sugar levels.
- Mild anaemia, mild eosinophilia.
- Plasma cortisol measured between 8 and 9 am <3 mg/dL suggests adrenal insufficiency while a level >19 μg/dL excludes it.
- ACTH stimulation test—There is failure of plasma cortisol to rise beyond 19 μg/dL following administration of 250 μg of synthetic ACTH.
- Plasma ACTH levels are elevated (>100 pg/dL) in primary adrenal insufficiency.

- PRA is high and plasma aldosterone levels are low or normal.
- In tuberculous adrenalitis, chest radiograph may show evidences of pulmonary tuberculosis. Plain radiograph of abdomen, CT scan and MRI scan may show adrenal calcification.
- Adrenal and other organ-specific antibodies (e.g. adrenal cortex antibodies, 21-hydroxylase antibodies) may be detected in the serum in autoimmune adrenalitis.

Management

- Patients with Addison's disease require lifelong glucocorticoid and mineralocorticoid replacement therapy.
- Cortisone is given at a dose of 20 mg on getting up in the morning and 10 mg in the evening at 6 pm. Alternatively, prednisolone is given in a dose of 5 mg in the morning and 2.5 mg in the evening.
- Fludrocortisone (mineralocorticoid) 0.05–0.1 mg daily in patients with primary adrenal insufficiency.
- Addison's disease due to tuberculous adrenalitis should be treated with antituberculous chemotherapy.
- During periods of stress and infections the patient should be told to take additional doses of prednisolone.

Q. Describe acute adrenal crisis.

- Adrenal crisis (acute adrenal insufficiency) can occur in a patient with primary adrenal insufficiency who has a serious infection or other acute stress.
- It can also occur after bilateral adrenal infarction or bilateral adrenal haemorrhage.
- Adrenal haemorrhage and often death has been associated with meningococcaemia (Waterhouse–Friderichsen syndrome).
- It is rare in patients with secondary adrenal insufficiency.

Clinical Features

- The predominant manifestation of adrenal crisis is shock, but the patients often have non-specific symptoms such as anorexia, nausea, vomiting, abdominal pain, weakness, fatigue, lethargy, confusion or coma.
- Two other common features are abdominal tenderness and fever.
- Patients with long-standing adrenal insufficiency who present in crisis may be hyperpigmented (due to chronic ACTH hypersecretion) and have weight loss, serum electrolyte abnormalities and other manifestations of chronic adrenal insufficiency.
- Loss of mineralocorticoid activity is associated with development of hypotension, hyponatraemia and hyperkalaemia.

Management

- Initiate therapy as soon as acute adrenal crisis is suspected.
- Correct hypovolaemia and sodium depletion with normal saline.
- Add 5% dextrose solution if the patient is hypoglycaemic.
- Administer hydrocortisone in a dose of 100 mg 6 hourly and taper it over 24–48 hours to a maintenance dose once the underlying stress resolves.

Q. What is the present role of steroid therapy?

Q. Discuss the use and abuse of steroids.

Q. What are the complications of corticosteroid therapy?

Q. How can you minimise the side effects of corticosteroid?

Equivalent Doses of Glucocorticoids (Anti-Inflammatory Potency)

- Hydrocortisone (cortisol)—20 mg
- Cortisone acetate—25 mg
- Prednisolone—5 mg
- Methylprednisolone—4 mg
- Betamethasone—0.75 mg
- Dexamethasone—0.75 mg

- Prednisolone has only 25% of mineralocorticoid activity as compared to that of hydrocortisone while dexamethasone and betamethasone have negligible mineralocorticoid activity.

Common Indications of Steroids

- Bronchial asthma, raised intracranial tension, cerebral oedema, rheumatoid arthritis, SLE, other connective tissue diseases, nephrotic syndrome, adrenal insufficiency, shock, septicaemia, leukaemia, lymphoma, as an adjunct in chemotherapy for malignancies, carditis, demyelinating diseases, tuberculosis of pericardium and tuberculous meningitis.

Common Contraindications of Steroids

- Active tuberculosis, peptic ulcer, bleeding tendencies, diabetes, uncontrolled hypertension, any active infection, etc.

Side Effects of Corticosteroid Therapy

- Side effects of corticosteroid therapy can be considered under two headings:
  1. Metabolic effects.
  2. Suppression of the hypothalamic–pituitary–adrenal axis (HPA axis).

Metabolic Effects

- Cushingoid features (refer Cushing's syndrome).
- Mood changes ranging from euphoria (steroid psychosis) to depression.
- Fluid retention and oedema.
- Hypertension.
- Glucose intolerance or frank diabetes mellitus.
- Osteoporosis, bone pains and fractures.
- Increased susceptibility to infections.
- Re-activation of latent tuberculosis.
- Impaired wound healing.
- Gastric erosions.
- Masked perforation.
- Haemorrhage from stomach and duodenum.

Suppression of Hypothalamic–Pituitary–Adrenal Axis

- Occurs with high-dose therapy.
- This makes it difficult to withdraw steroids.
- Can be minimised by giving steroids as a single morning dose or better, on alternate days.

Measures to Reduce the Side Effects

• Giving the lowest possible dose	• Giving only under medical supervision
• Giving on alternate days rather than daily	• Monitoring caloric intake to prevent weight gain
• Giving as a single dose rather than in divided doses	• Reducing sodium intake
• Giving in the morning rather than at any other time	• Using H_2 receptor blockers or proton-pump inhibitors
• Giving for the shortest possible duration	• Providing high calcium intake and vitamin D
• Giving for established indications only	• Using biphosphonates

Q. Write briefly on Waterhouse–Friderichsen syndrome.

- Waterhouse–Friderichsen syndrome is characterised by acute haemorrhagic destruction of both the adrenal glands, usually associated with fulminant meningococcal septicaemia. It is characterised by vasomotor collapse and shock.

- Onset is abrupt and profound prostration occurs within a few hours. Petechiae, purpuric lesions and haemorrhage into the skin occur.
- Early in the pre-shock stage, there is generalised vasoconstriction and the patient looks alert and pale, with circumoral cyanosis and cold extremities.
- In the shock stage, coma develops, cardiac output falls and blood pressure drops. If untreated, patient dies of cardiac and/or respiratory failure.

Q. Give a brief account of phaeochromocytoma.

- Phaeochromocytoma is a tumour of the chromaffin tissue that secretes catecholamines (adrenaline and noradrenaline).
- Paraganglioma is an extra-adrenal tumour that arises from both sympathetic and parasympathetic paraganglia, located anywhere from the base of the skull to the pelvis.
- 90% of the tumours arise from the adrenal medulla (phaeochromocytoma), while 10% are paragangliomas.
- 90% of pheochromocytomas are unilateral, while 10% are in bilateral adrenals.
- 90% are benign while 10% are malignant.
- Neurofibromatosis type 1 is associated with an increased incidence of phaeochromocytoma.
- Pheochromocytoma is seen in up to 50% of patients with MEN2 and in 10–20% of patients with von Hippel–Lindau syndrome.

Clinical Features

- Paroxysmal hypertension associated with episodes of pallor or flushing, palpitations, sweating, headache and anxiety (fear of death). However, sustained hypertension is more common than paroxysmal hypertension.
- Gastrointestinal symptoms like abdominal pain, vomiting, constipation and weight loss.
- Glucose intolerance.
- Complications of hypertension like stroke, myocardial infarction, cardiomyopathy and left ventricular failure.
- May be associated with multiple endocrine neoplasia type 2 (MEN-2).

Investigations

- 24-hour urine vanillylmandelic acid (VMA) is raised (less sensitive and specific compared to other tests).
- 24-hour urine metanephrines and normetanephrines are raised.
- 24-hour urine free catecholamines are raised.
- Plasma noradrenaline and adrenaline levels are raised.
- Chromogranin A (a major secretory protein present in the soluble matrix of chromaffin granules) is elevated.
- Provocative (glucagon provocation test), suppressive (clonidine suppression test) and adrenolytic (phentolamine test) tests are rarely required.
- CT scan to localise tumour.
- Scintigraphy to localise tumour.
  - MIBG (^{123}I-labeled meta-iodobenzylguanidine) scintigraphy.
  - Somatostatin receptor scintigraphy using ^{111}indium-labeled diethylenetriaminepentaacetic acid octreotide scan.
  - [^{18}F]fluorodihydroxyphenylalanine (DOPA) PET scan.
  - Selective venous sampling with measurement of plasma noradrenaline can localise tumour in difficult cases.

Management

- Excision of the tumour if possible.
- If excision is not possible, long-term treatment with α- and β-adrenoreceptor blocking drugs (phenoxybenzamine and propranolol, or labetalol) is advocated. β-blockers should never be given alone.

Q. What is impotence? Discuss briefly.

- Male sexual dysfunction is termed impotence. It may manifest in various ways like loss of desire, inability to obtain and maintain erection, premature ejaculation, absence of emission and inability to achieve orgasm.

- Erectile impotence could be of various causes, but majority are due to psychological causes. In every case of erectile impotence it is mandatory to rule out the following organic causes:

  - Endocrine causes—e.g. testicular failure, hyperprolactinaemia
  - Drugs—e.g. antihistamines, antihypertensives, anticholinergics, antidepressants, antipsychotics, tranquillisers, alcohol
  - Penile diseases
  - Neurologic diseases
  - Vascular disease—e.g. Leriche syndrome

Q. Describe the classification and causes of diabetes mellitus (DM).

- Diabetes mellitus (DM) is a clinical syndrome characterised by hyperglycaemia due to absolute or relative deficiency of insulin, or both (i.e. defects in insulin secretion, insulin action or both).

Aetiological Classification

Type 1 diabetes	Other specific types of diabetes
- Type 1A (immune-mediated)	- Genetic defects of β-cell function (maturity onset diabetes of the young, MODY)
- Type 1B (idiopathic)	- Genetic defects in insulin action (e.g. type A insulin resistance, lipoatrophic diabetes)
Type 2 diabetes	- Diseases of exocrine pancreas (pancreatitis, pancreatectomy, pancreatic neoplasm, haemochromatosis, fibrocalculus pancreatopathy)
	- Other endocrine diseases (acromegaly, Cushing's syndrome, glucagonoma, phaeochromocytoma, hyperthyroidism)
	- Infections (congenital rubella, cytomegalovirus)
	- Drug/toxin-induced (vacor, glucocorticoids, pentamidine, diazoxide, T_4, β agonists, thiazides, protease inhibitors, α-interferon, nicotinic acid)
	- Insulin receptor defects or insulin receptor antibodies
	- Other genetic syndromes (Down's syndrome, Klinefelter's syndrome, Turner's syndrome, myotonic dystrophy, porphyria, Friedreich's ataxia)
	Gestational diabetes mellitus (GDM)

- The two broad categories of DM are designated type 1 (NOT type I) and type 2 (NOT type II).
- In type 1 DM, there is absolute insulin deficiency. Type 1 is subdivided into two groups: type 1A due to cell-mediated autoimmune destruction of β-cells and type 1B where β-cell destruction occurs due to unknown cause. It most often occurs in younger patients but nearly 10% of patients above the age of 30 years have this type of DM.
- In type 2 DM, there are variable degrees of insulin resistance, impaired insulin secretion and increased glucose production. It also occurs due to several genetic and metabolic syndromes. Some children have type 2 DM.
- The terms insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM) are no longer used because several patients with NIDDM eventually would require insulin.
- Maturity onset of diabetes in the young (MODY) is characterised by autosomal dominant inheritance, early onset of diabetes, impairment of insulin secretion and lack of autoantibodies.

Q. Briefly outline the pathogenesis of diabetes mellitus.

Pathogenesis of Type 1 Diabetes Mellitus

- Type 1 diabetes appears when more than 90% of β-cells of pancreas are destroyed by an autoimmune process. The pathogenetic sequence is given below.
- First, genetic susceptibility to the disease must be present. About 95% of patients with type 1 DM have either HLADR3 and/or DR4. Despite this, most individuals with type 1 DM do not have a first-degree relative with diabetes.

- Second, an environmental event (commonly viral infection) initiates the process in genetically susceptible individuals.
- Third step in the sequence is an inflammatory response in the pancreas called "insulitis". There is infiltration of the islets with activated T lymphocytes.
- Fourth step is the activation of autoimmunity. There is an alteration of the surface of the β-cell such that it is no longer recognised as "self", but is seen by the immune system as a foreign cell or "non-self".
- Fifth step is the development of an immune response. Though islet cell antibodies (ICA) and several other autoantibodies are present in most patients, they are not involved in destructive process. Instead, activated T lymphocytes present in the islets release cytokines (tumour necrosis factor α, interferon γ and interleukin 1) that destroy β-cells. CD8 + cell-induced cytotoxicity and apoptosis are also involved. This results in an immune attack on β-cells, with resultant destruction of β-cells. When more than 90% of β-cells are destroyed, diabetes appears. α-cells remain intact.

Genetic susceptibility

↓

Environmental event

↓

Insulitis

↓

Activation of autoimmunity

↓

Immune attack on beta-cells

↓

Diabetes mellitus
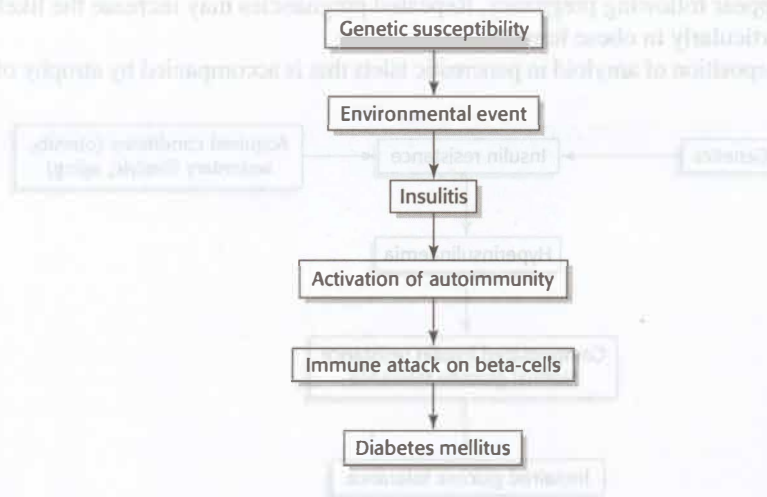
- The events that trigger the transition from glucose intolerance to frank diabetes are often associated with increased insulin requirements that might occur during stress, infection or puberty. Thus, following initial development of frank DM, many patients become euglycaemic without need of insulin for sometime. This is called "honeymoon phase". This generally lasts for a few months after which the patient develops frank DM again.
- Markers of immune destruction of the β-cells include islet cell autoantibodies, autoantibodies to insulin, autoantibodies to glutamic acid decarboxylase (GAD65), and autoantibodies to the tyrosine phosphatases IA-2 and IA-2β. One and usually more of these autoantibodies are present in 85–90% of individuals when fasting hyperglycaemia is initially detected.
- The disease also has strong HLA associations with linkage to the DQA and DQB genes, and it is influenced by the DRB genes. These alleles can be either predisposing or protective.
- These patients are also prone to other autoimmune disorders such as Graves' disease, Hashimoto's thyroiditis, Addison's disease, vitiligo, coeliac sprue, autoimmune hepatitis, myasthenia gravis and pernicious anaemia.

Idiopathic type 1 Diabetes Mellitus

- This form of diabetes is strongly inherited, lacks immunological evidence for β-cell autoimmunity and is not HLA associated.

Pathogenesis of Type 2 Diabetes Mellitus

- In contrast to type 1 DM, in type 2 DM no HLA relationship has been identified and autoimmune mechanisms are not operative.
- Genetic influence is much more powerful in type 2 DM than in type 1 DM.
- Pancreatic β-cell mass is intact in type 2 DM, in contrast to the situation with type 1 DM. The α-cell population is increased.
- Certain factors need to be considered in the pathogenesis of type 2 diabetes. They are:
  - Type 2 DM is associated with increased hepatic production of glucose, resistance to the action of insulin and impaired insulin secretion. Insulin resistance may be due to any one of three general causes: an abnormal insulin molecule, an excessive amount of circulating antagonists and target defects. The last is the most common cause of insulin resistance in type 2 DM.

- The defects in the receptors present in target tissues is generally at the post-receptor level.
- Reduced utilisation of glucose by peripheral tissues (mostly skeletal muscles) results in post-prandial hyperglycaemia while increased hepatic glucose output produces fasting hyperglycaemia.
- In the early stages glucose tolerance remains normal despite insulin resistance. This is due to compensatory increase in insulin secretion by β-cells. As insulin resistance and compensatory hyperinsulinaemia progress the β-cells become unable to sustain this hypersecretion. This results in impaired glucose tolerance and later frank DM. Ultimately, β-cell failure develops.
- Over-eating, especially when combined with obesity and underactivity, is associated with the development of type 2 DM.
- Ageing is an important risk factor for type 2 DM.
- In females who are genetically predisposed pregnancy may be associated with the development of hyperglycaemia. It may or may not disappear following pregnancy. Repeated pregnancies may increase the likelihood of developing permanent diabetes, particularly in obese females.
- In type 2 DM, there is deposition of amyloid in pancreatic islets that is accompanied by atrophy of islet epithelial cells.
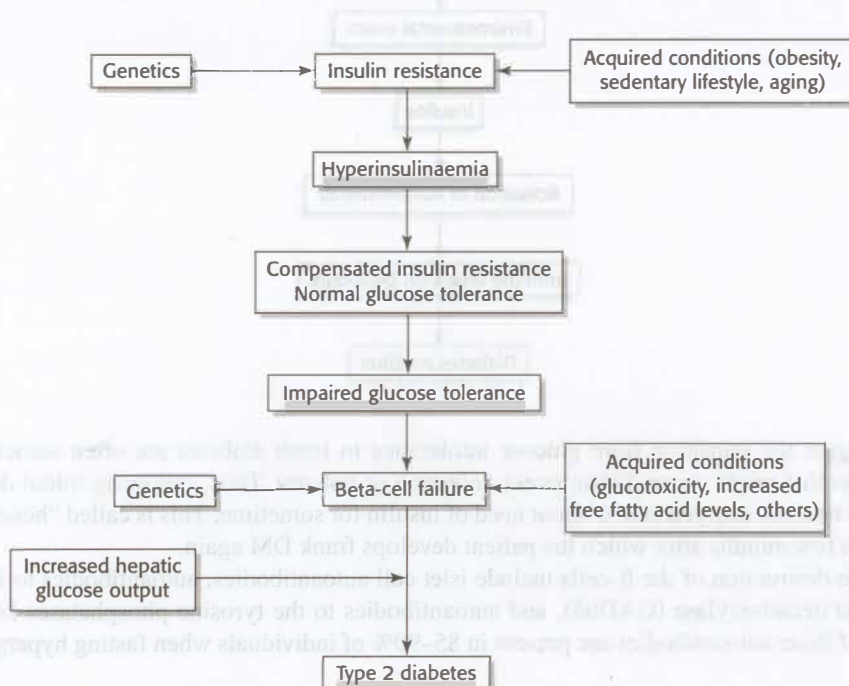
Q. What are the clinical features of diabetes mellitus?

Q. Describe potential diabetes and latent diabetes.

- Typically, the clinical features of type 1 and type 2 DM are distinctive. A comparison of the clinical features is given in the table below.

Type 1 DM

- Usually begins before the age of 40.
- Body habitus is normal to wasted.
- The onset of symptoms may be abrupt, with polyuria, polydipsia, polyphagia and weight loss developing over days or weeks.
- Some cases may present as ketoacidosis during an intercurrent illness or following surgery.
- Occasionally, an initial episode of ketoacidosis is followed by a symptom-free interval ("honeymoon period") during which no treatment is required.
- Characteristically, the plasma insulin is low or unmeasurable. Glucagon levels are elevated but suppressible with insulin.

Type 2 DM

- Usually begins after the age of 40.
- The typical patient is obese.
- The symptoms begin gradually, over a period of months to years. Frequently, hyperglycaemia is detected in an asymptomatic person on a routine examination. Many patients will present with one of the chronic complications of diabetes and on investigations are found to be diabetic.
- These patients usually do not develop ketoacidosis. In the decompensated state, they are susceptible to the syndrome of hyperosmolar hyperglycaemic state (hyperosmolar non-ketotic coma).
- The plasma insulin levels are normal to high. Glucagon levels are elevated, but resistant to insulin.

General Characteristics

Feature	Type 1 DM	Type 2 DM
• Age of onset	<40 years	>40 years
• Duration of symptoms	Days or weeks	Months or years
• Body habitus	Normal to wasted	Obese
• Plasma insulin	Low to absent	Normal to high
• Plasma glucagon	High, suppressible	High, resistant
• Acute complication	Ketoacidosis	Hyperosmolar hyperglycaemic state
• Insulin therapy	Responsive	Responsive to resistant
• Sulphonylurea therapy	Unresponsive	Responsive
• Autoantibodies	Yes	No
• Other autoimmune diseases	Yes	No
• Family history of diabetes	No	Yes

Potential Diabetics

- Potential diabetics are persons with a normal glucose tolerance test who have an increased risk of developing diabetes for genetic reasons. Examples are:
  - Children of two diabetic parents.
  - Sibling of a diabetic.
  - Non-diabetic member of a pair of monozygotic twins where the other is a diabetic.

Latent Diabetics

- Latent diabetics are persons in whom the glucose tolerance test is normal but who are known to have given an abnormal result under conditions imposing a burden on the pancreatic cells—e.g. during pregnancy, infection, severe stress (physical or mental), during treatment with corticosteroids, thiazide diuretics or other diabetogenic drugs, or when overweight.

Q. Discuss briefly the diagnosis of diabetes mellitus.

Q. Explain what is impaired fasting glucose (IFG).

Q. Write briefly on impaired glucose tolerance.

- Diabetes may present with polyuria, polydipsia, polyphagia and significant weight loss despite polyphagia.
- Depressed immune status may result in flare-ups of pulmonary tuberculosis, non-healing of wounds, recurrent styes, candidial pruritus vulvae, balanitis and recurrent urinary tract infections.
- Some patients may present with end-organ involvement—e.g. retinopathy, nephropathy or neuropathy.
- In some cases, risk factors may be identifiable—e.g. obesity, pregnancy and first-degree relatives of known diabetics.
- Urine examination may show glycosuria with or without ketonuria.
- Glycosylated haemoglobin (HbA_1) levels may be elevated (normal <6%).
- HLA typing may reveal the genetic predisposition in type 1 diabetes mellitus.

Diagnostic Criteria

Diabetes mellitus
- Symptoms of diabetes plus random plasma glucose >200 mg/dL (symptoms of diabetes plus random whole blood glucose >175 mg/dL)

OR

- Fasting plasma glucose ≥125 mg/dL (fasting whole blood glucose ≥110 mg/dL)

OR

- 2-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test (OGTT) (whole blood ≥175 mg/dL during an oral 75 g glucose tolerance test)

OR

- Glycated haemoglobin (HbA1c) ≥ 6.5%

In the absence of unequivocal hyperglycaemia or presence of acute metabolic decompensation, these criteria should be confirmed by repeat test

Impaired fasting glucose (IFG)
- Fasting plasma glucose ≥100 mg/dL but <125 mg/dL (whole blood glucose ≥88 mg/dL but <110 mg/dL)

Impaired glucose tolerance (IGT)
- Plasma glucose between 140 and 200 mg/dL 2 hours after oral glucose load (whole blood glucose between 125 and 175 mg/dL 2 hours after oral glucose load)

Normal glucose levels
- Fasting plasma glucose <100 mg/dL (whole blood glucose <88 mg/dL)
- 2-hour post-prandial or post-oral glucose tolerance test <140 mg/dL (whole blood glucose <125 mg/dL)

- In the absence of pregnancy, IFG and IGT are not clinical entities in their own right but rather risk factors for future diabetes as well as cardiovascular disease. Both have been termed "pre-diabetes". Additionally, HbA1c in the range of 5.7–6.4% is also included in "pre-diabetes". The term "pre-diabetes" has been changed to "categories of increased risk for diabetes".
- IFG and IGT are associated with the metabolic syndrome, which includes obesity (especially abdominal or visceral obesity), dyslipidaemia of the high-TG and/or low-HDL type, and hypertension.
- Medical nutrition therapy aimed at producing 5–10% loss of body weight, exercise and certain pharmacological agents (acarbose, metformin) have been variably demonstrated to prevent or delay the development of diabetes in people with IGT.
- At the time of diagnosis, assess the patient completely, particularly blood pressure, possible diabetes complications such as neurologic and foot examinations, lipid profile, urine microalbumin:creatinine ratio, and an ophthalmologic assessment to evaluate for retinopathy.
- The goal of treatment is to achieve HbA1c ≤6.5% or HbA1c >6.5% if lower target cannot be achieved without adverse outcomes.

Q. Write briefly on Benedict's test.

Q. Describe renal glycosuria and Marble's criteria for diagnosis of renal glycosuria.

Q. What is meant by alimentary (lag storage) glycosuria?

Q. Discuss the differential diagnosis of glycosuria.

Benedict's Test

- Benedict's qualitative reagent contains copper sulphate, sodium potassium citrate or tartrate (Rochelle salt), and sodium carbonate.
- Principle.
  - When a reducing sugar solution is heated with Benedict's solution, the reducing sugar under alkaline conditions tautomerise to form erediols. The erediols are unstable and decompose to yield short-chain aldehydes. Short-chain aldehydes are powerful reducing agents that reduce the cupric ions to cuprous ions.

- Procedure.
  - To 5 mL Benedict's qualitative reagent, 8–10 drops of protein free urine is added and the mixture is boiled for 2 minutes and allowed to cool. If a reducing substance is present, a precipitate will appear, varying from light green turbidity to a red precipitate. If the reducing substance is glucose the test gives approximately quantitative results.
    - Light green turbidity—0.1–0.5 g/dL sugar
    - Green precipitate—0.5–1.0 g/dL sugar
    - Yellow precipitate—1.0–2.0 g/dL sugar
    - Red precipitate—≥2.0 g/dL sugar

Differential Diagnosis of Glycosuria

- When glycosuria (melituria) is found, it should be determined whether it is secondary to hyperglycaemia (diabetes mellitus) or non-diabetic glycosuria. In diabetics, glycosuria occurs when blood glucose level exceeds the renal glucose threshold of 180 mg/dL.
- Non-diabetic melituria occurs in a number of conditions, the most important being renal glycosuria and alimentary (lag storage) glycosuria.

Renal Glycosuria

- Diagnosis of renal glycosuria is based on the Marble's criteria.
  - Glycosuria in the absence of hyperglycaemia.
  - Constant glycosuria with little fluctuation related to diet.
  - Normal OGTT.
  - Identification of urinary reducing substance as glucose.
  - Normal storage and utilisation of carbohydrates.

Alimentary (Lag Storage) Glycosuria

- Here, there is a transient abnormal rise in blood glucose level following a meal, and the concentration exceeds the normal renal threshold. During this time glucose spills into the urine. This may occur in the following conditions:
  - Following gastric surgery with rapid gastric emptying time.
  - Some normal people.
  - Hyperthyroidism.
  - Hepatic diseases.

Q. Give a brief account of oral glucose tolerance test (OGTT) and impaired glucose tolerance (IGT).

- The patient, who should have been taking an unrestricted carbohydrate diet for at least 3 days or more prior to the test, fasts overnight (at least 8 hours).
- The patient should rest for at least half an hour before starting the test, and refrain from smoking during the test.
- A sample of blood is drawn to estimate the fasting glucose level.
- A glucose load of 75 g dissolved in 300 mL of water is given orally.
- Blood samples are withdrawn at half-hourly intervals for 2 hours (1/2 hour, 1 hour, 1½ hour, 2 hour) and glucose levels are estimated.
- Patients with impaired glucose tolerance are at increased risk for the development of DM or fasting hyperglycaemia.
- The criteria for IGT have been given previously.

Q. Discuss briefly the dietary management of diabetes mellitus.

Q. Describe medical nutrition therapy in diabetes.

- People with diabetes should receive individualised dietary advice (medical nutrition treatment) as needed to achieve treatment goals. Medical nutrition diet and physical exercise activate cellular mechanisms which protect by improving mitochondrial function, reducing generation of radicals and improving efficacy of insulin.
- The preparation of a dietary regimen for a diabetic can be considered under three steps.

First Step

- This involves the estimation of the total daily caloric requirement of the individual patient. This must be estimated after considering a number of variable factors like age, sex, actual weight, desirable weight, activity and occupation of the patient. However, an approximate total daily caloric requirement can be calculated as:
  - Sedentary individuals—30 Kcal/kg/day
  - Moderately active individual—35 Kcal/kg/day
  - Heavily active individuals—40 Kcal/kg/day

Second Step

- This involves allocation of the calories in a proper proportion to carbohydrate, protein and fat. The recommended proportion of calories to be derived from each of them is given as:
  - Carbohydrate—50–65%.
  - Protein—10–20%.
  - Total fat—25–30%.
    - Saturated fat—≤7%.
    - Polyunsaturated fat—≤10%.
    - Monounsaturated fat—10–15%.
- However, a few more important factors need be considered at this stage. They are:
  - The minimal protein requirement for a good nutritious diet is about 0.9 g/kg/day.
  - The carbohydrates should be taken in the form of starches and other complex sugars. Rapidly absorbed simple sugars like glucose and even sucrose should generally be avoided. Use of non-caloric sweeteners (non-nutritive sweeteners) like acesulfame potassium, aspartame, neotame, saccharin and sucralose is acceptable.
  - Fish oils containing omega-3 fatty acids have been reported to be beneficial as antiatherogenic.
  - A high-fibre diet is beneficial as it has an antiatherogenic effect mediated through lowering of blood lipids.

Third Step

- This involves distribution of the calories throughout the day. This is particularly important in insulin-requiring diabetics to avoid hypoglycaemia. Different distributions may be required for different lifestyles. However, a typical pattern of distribution of calories is:
  - 20% of the total calories—for breakfast
  - 35% of the total calories—for lunch
  - 30% of the total calories—for dinner
  - 15% of the total calories—for late-evening feed

Q. What are oral antidiabetic drugs? Discuss their mechanism of actions and indications.

- Oral antidiabetic drugs (previously called hypoglycaemic drugs) fall into the following categories:
  - Sulphonylureas
  - Meglitinide
  - Biguanides
  - α-glucosidase inhibitors
  - Thiazolidinediones
  - Incretin-based therapy
  - Other drugs

Sulphonylureas

Mechanism of Action

- Sulphonylureas are insulin secretagogues, i.e. they stimulate insulin secretion by blocking the opening of ATP-sensitive potassium channels on the β-islet cells. This leads to a depolarisation of the membrane, leading to an influx of calcium. These events result in an increased production of insulin by the β–cell.
- Contrary to previously held belief, they do not increase insulin sensitivity and, therefore, should be avoided in type 1 DM.

Indications

- Sulphonylureas are effective in the treatment of non-obese patients with type 2 DM who fail to respond to dietary measures alone.

Comparative Features

Drug	Daily dose (mg)	Doses/day	Half-life (hours)	Metabolism/excretion
First generation				
• Acetohexamide	500–1500	1–2	5	Liver/kidney
• Chlorpropamide	100–500	1	36	Kidney
• Tolbutamide	500–3000	2–3	4	Liver
• Tolazamide	100–750	1–2	7	Liver
Second generation				
• Glibenclamide	2.5–20	1–2	12	Liver/kidney
• Gliclazide	40–320	1–2	10-12	Liver/kidney
• Glipizide	2.5–30	1–2	3.5	Liver/kidney
• Glyburide	1.25–20	1–2	12-14	Liver/kidney
• Glimepiride	1–8	1	5-8	Liver/kidney

Special Points

- The first generation sulphonylureas have longer half-life, greater incidence of hypoglycaemia and more frequent drug interactions compared to the second generation sulphonylureas. Therefore, second generation drugs are preferred.
- They increase the insulin secretion acutely, and hence, should be taken shortly before a meal.
- As these drugs are metabolised in liver and then excreted through kidneys, they should be avoided in the presence of significant renal or liver dysfunction.
- Common side effects include hypoglycaemia (which may be prolonged) and weight gain (due to increased insulin levels and control of DM).
- Hypoglycaemia occurring with sulphonylureas (particularly chlorpropamide and glibenclamide) tends to be severe and prolonged.
- In patients with significant renal disease, it is preferable to use tolbutamide or tolazamide, as these agents are exclusively metabolised by the liver.
- Chlorpropamide has a long biological half-life of about 36 hours and hence, has the advantage that it can be given as a single dose at breakfast. However, it has significant side effects like prolonged and severe hypoglycaemia, cholestatic jaundice, SIADH, skin rashes and a disulfiram-like reaction in patients after taking alcohol.
- Some sulphonylureas have significant interactions with other medications such as warfarin, aspirin, ketoconazole and alcohol.
- Some patients do not respond to sulphonylureas, and these are termed "primary treatment failures". Some patients respond initially to sulphonylureas, but then cease to respond in the next year or two. These are termed "secondary treatment failures". Dietary non-compliance is the most common cause of secondary treatment failure.

Meglitinide

- These drugs also act on ATP-sensitive potassium channel to increase insulin secretion.
- Examples include repaglinide and nateglinide.
- Because of its short half-life repaglinide is given with or immediately before each meal to reduce meal-related glucose excursions.
- Dose is 0.5–16 mg/day.
- It should be avoided in presence of significant liver dysfunction.

Biguanides

- Metformin is the only drug used in this group (the other agent, phenformin is no longer used because of associated side effects).

Mechanism of Action

- The main effect is to reduce the hepatic glucose production.
- Minor effect is to improve the peripheral glucose utilisation.

Indications

- As metformin does not produce weight gain, it is particularly useful in obese patients with type 2 DM who do not respond to dietary measures and weight reduction.
- In primary and secondary treatment failures with sulphonylureas, metformin may be added.

Special Points

- It reduces the fasting blood glucose and insulin levels, promotes modest weight loss and improves the lipid profile (reduction in fasting TG levels and LDL).
- It is started at a dose of 500 mg twice daily and gradually increased to a maximum of 1 g thrice daily. Sustained-release preparations are also available and need to be given once or twice a day.
- Its main side effect is acidosis that can be prevented if it is not used in some situations like presence of renal impairment (creatinine >1.4 mg/dL), congestive failure, liver disease, severe hypoxia or pre-existing acidosis.
- Other side effects are anorexia, diarrhoea and metallic taste in mouth.
- As it is not an insulin secretagogue, it is not usually associated with hypoglycaemia.

α-glucosidase Inhibitors

- This group includes acarbose, miglitol and voglibose.

Mechanism of Action

- α-glucosidase is an enzyme located on the brush border of the intestine. It is required for the breakdown of disaccharides to form single sugars before carbohydrates can be absorbed. Acarbose and other agents inhibit the α-glucosidase enzymes. This leads to poor absorption of carbohydrates thereby causing reduced rise in post-prandial blood glucose.

Indications

- These agents are useful in managing patients who develop significant post-prandial hyperglycaemia but otherwise have relatively well-controlled blood glucose levels.

Special Points

- Dose of both acarbose and miglitol is 25 mg with evening meal first. This can be gradually increased to 50 mg with each meal. Dose of voglibose is 0.2–0.3 mg with each meal.
- These agents are poorly tolerated because of fermentation of unabsorbed carbohydrates in the large intestine. This produces diarrhoea, flatulence and abdominal distension. However, increased disaccharide concentration leads to the induction of α-glucosidase enzymes (disaccharidases) in the jejunum and ileum. Eventually, this induction of new enzymes results in a slower, smoother absorption of disaccharides. The slower absorption is still effective in reducing post-prandial glucose levels, but with fewer malabsorptive symptoms. Therefore, α-glucosidase inhibitors must be started at a very low dose, with small increments over time.
- The blood levels of sulphonylureas may increase if administered simultaneously.
- These agents do not cause hypoglycaemia.
- They do not undergo renal excretion so that they are safe in patients with a modest elevation of serum creatinine. However, these agents should be avoided if creatinine >2.0 mg/dL and also in inflammatory bowel disease.

Thiazolidinediones

- This group includes pioglitazone. Rosiglitazone, the other agent has been withdrawn due to increased incidence of acute myocardial infarction and cardiovascular deaths in patients using it.

Mechanism of Action

- Pioglitazone binds to peroxisome proliferator-activated receptor (PPAR-γ), a nuclear receptor that regulates transcription of genes involved in lipid metabolism and insulin action. This promotes adipocyte differentiation and reduced insulin resistance in skeletal muscles.
- Due to reduction in insulin resistance, it increases peripheral glucose utilisation. It may also reduce hepatic glucose production.

Special Points

- Dose of pioglitazone is 15–45 mg/day.
- Can be combined with metformin and sulphonylureas.
- Maximum effect may be seen only after 3–4 weeks.
- Liver functions should be monitored periodically as liver dysfunction may develop.
- Important side effects include weight gain (due to water retention as well as increase in adiposity) and mild rise in LDL. HDL levels may increase.
- Contraindicated in liver disease and congestive cardiac failure.
- May produce fluid retention, cardiac insufficiency and increased propensity to bone fractures.

Incretin-Based Therapy

- Incretin hormones, primarily glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are polypeptide hormones synthesised in gut. GIP and GLP-1 are secreted by enteroendocrine K-cells in the proximal gut and L-cells in the distal gut respectively. These act on their receptors present on islet cells to stimulate insulin secretion in response to food. This potentiation of insulin secretion by the gut is referred to as the *intestinal secretion of insulin* or incretin effect—increase in insulin is markedly greater in response to an oral than to an intravenous glucose challenge.
- In addition, they enhance β-cell proliferation and promote resistance to apoptosis.
- GLP-1 also lowers plasma glucose levels through inhibition of glucagon secretion, deceleration of gastric emptying and inhibition of food intake. It also provides cardioprotective and vasodilatory effects.
- Insulin modulatory properties of GIP are attenuated in patients with type 2 diabetes; hence in clinical practice only GLP-1 analogues are used.
- GLP-1 as well as GIP are rapidly degraded in the circulation by dipeptidyl peptidase IV.
- Various analogues of GLP-1 and inhibitors of dipeptidyl peptidase IV have been developed. These are known as incretin mimetics.

Glucagon-like Peptide-1 Analogues

- Exenatide, liraglutide and albiglutide have been approved for use in combination with metformin, a sulphonylurea, or a thiazolidinedione. They produce weight loss.
- These analogues need to be given parenterally.
- Risk of hypoglycaemia is low.
- Adverse effects include nausea, diarrhoea and rarely pancreatitis.

Dipeptidyl Peptidase IV Inhibitor

- An alternative approach to the use of GLP-1 analogues is to inhibit dipeptidyl peptidase IV to conserve endogenous GLP-1.
- Vildagliptin, sitagliptin, sexagliptin, linagliptin and alogliptin are oral agents for use in type 2 diabetes mellitus either as monotherapy or with other agents. Risk of hypoglycaemia is low.
- Side effects include nausea, diarrhoea, headache, upper respiratory symptoms and possible risk for pancreatitis.

Others

- Pramlintide, a synthetic form of pancreatic hormone amylin, is to be injected before each meal. Amylin is a hormone co-secreted with insulin, and regulates glucose influx through the suppression of glucagon and slowing of gastric emptying. The most common side effects are nausea and hypoglycaemia.
- Sodium-glucose co-transporter 2 (SGLT2) inhibitors like dapagliflozin reduce renal glucose resorption and thus cause glycosuria and a resulting insulin-independent reduction in blood glucose as well as weight loss. SGLT-2 inhibitors do not confer any risk of hypoglycaemia but produce increased incidence of genital infections.

Q. Describe briefly the role of insulin in the management of diabetes.

Q. How do you classify insulins? Give a brief account of the commonly used insulins.

Q. Discuss briefly about pancreatic transplantation.

- Insulin is required for treatment of all patients with type 1 DM and many patients with type 2 DM. The goals of insulin therapy are:
  - Normal growth and development in children.
  - Normal pregnancy, delivery and conceptus in females.
  - Minimal interference with psychological adjustment.
  - Acceptable glycaemic control, with minimal hypoglycaemia.
  - Prevention of complications.

General Indications for Insulin Therapy

- Type 1 DM.
- Diabetic ketoacidosis (DKA).
- Hyperosmolar hyperglycaemic state (previously called non-ketotic hyperglycaemic coma).
- Stress of surgery, infections and trauma.
- Diabetes during pregnancy.
- Non-obese type 2 DM unresponsive to oral drugs.
- Post-renal transplantation diabetic patients.

Insulin Preparations

- Insulin preparations can be classified in different ways:
  - Based on source as bovine, porcine and human insulins.
  - Based on purity as conventional, single peak and monocomponent insulins.
  - Based on time course of action as rapid, intermediate and long-acting insulins.
  - Based on strength as 40 and 100 units/mL.
  - Newer insulin analogues.

Purification of Porcine Insulin

Crystallisation

- Processing of conventional insulin on gel chromatography reveals the impurities as three peaks—"a", "b" and "c" peaks.
  - The "a" peak is due to pancreatic proteins of high molecular weight (>12,000).
  - The "b" peak is due to proinsulin and intermediates.
  - The "c" peak is due to insulin fragments (derivatives) and pancreatic hormones (glucagon, somatostatin and pancreatic polypeptides).
- Crystallisation removes the "a" peak to a large extent and results in an insulin preparation of conventional purity. As this conventional insulin contains significant contaminants (proinsulin), it is highly immunogenic and can result in the development of anti-insulin antibodies.

Gel Filtration

- Insulin processed by gel chromatography results in a preparation known as "single peak" insulin (highly purified insulin).

Ion Exchange Chromatography

- Insulin purified by ion exchange chromatography results in the purest insulin preparation. This insulin preparation is hence known as monocomponent insulin.
- The advantages of monocomponent insulin are that it is less immunogenic, and causes less of lipodystrophy and insulin resistance.
- The indications for monocomponent insulin are:
  - Allergic reaction to conventional insulin.
  - Treatment of insulin resistance.
  - Treatment of lipodystrophy.
  - In pregnancy, to prevent transplacental transfer of antibodies, which can damage the foetal pancreas.
  - Liver disease.
  - As a short-term therapy in type 2 patients, to tide over surgery.

Human Insulin

- Human insulin differs from porcine insulin by one amino acid residue and from bovine insulin by three amino acid residues. The changes in the amino acid residues of these three insulins are given in the Table.

Amino acid position	A8	A10	B30
- Human	Threonine	Isoleucine	Threonine
- Porcine	Threonine	Isoleucine	Alanine
- Bovine	Alanine	Valine	Alanine

- Bovine insulin is more immunogenic than porcine insulin that is more immunogenic than human insulin. As the amino acid sequence of human insulin is known, it can be completely synthesised step by step. There are two types of human insulins.
  - Semisynthetic human insulin. This is an enzymatically modified pork insulin. The monocomponent porcine insulin is enzymatically de-alaninated from the B30 position, which is then replaced by threonine to make the structure identical to human insulin.
  - Highly purified human insulin is now available as a product of recombinant DNA biosynthesis.
- Human insulin is more rapidly absorbed and has a shorter duration of action compared to porcine or bovine regular insulin.

- Presently, the cost of human insulin is nearly the same as that of animal insulin. Therefore, many physicians are using them as the initial choice in diabetics requiring insulin.

Properties of Various Insulin Preparations

- The commonly used insulin preparations are classified based on their time of course of action into rapid, intermediate and long-acting insulins. Their properties are given below:

Class	Type	Peak effect (hours)	Duration of action (hours)
Rapid	Regular (crystalline, soluble, plain)	2–4	6–8
	Semilente	2–6	10–12
Intermediate	Isophane (NPH)	6–12	18–24
	Lente	6–12	18–24
Long-acting	Protamine zinc (PZI)	14–24	36
	Ultralente	18–24	36

- Lente (intermediate acting) insulin is simply a 30:70 mixture of semilente and ultralente, respectively.

Insulin Analogues

- These analogues are useful in patients who get repeated episodes of hypoglycaemia or show hyperglycaemia during some part of the day while on regular insulins.
- Insulin analogues have been prepared by modifying human insulin. Following preparations are available:
  - Lispro—Short-acting
  - Aspart—Short-acting
  - Glulisine—Short-acting
  - Glargine—Long-acting
  - Detemir—Long-acting
  - Degludec—Long-acting

Insulin Lispro

- It is a human insulin analogue created when the amino acids at positions 28 and 29 on the insulin B-chain are reversed. Like any other human insulin, it is produced by recombinant DNA technology utilising a non-pathogenic strain of *E. coli*.
- It is absorbed faster than regular human insulin, and therefore, has a more rapid onset of glucose-lowering activity (<15 minutes), an earlier peak for glucose lowering (60–90 minutes) and a shorter duration of glucose-lowering activity (<5 hours). Therefore, patient needs to take this insulin just before or after meals.
- However, it is equipotent to human regular insulin (i.e. 1 unit of insulin lispro has the same glucose-lowering capacity as 1 unit of regular insulin).
- Because of its short duration of action, it reduces the risk of hypoglycaemia several hours after meals.
- Patients require additional use of longer-acting insulin to maintain glucose control.

Insulin Aspart and Insulin Glulisine

- These are also short-acting insulin analogues that are similar to lispro.

Insulin Glargine

- It is a human insulin analogue that has a long duration of action (up to 24 hours) and has a pH of 4.
- It differs from human insulin in that there is an amino acid substitution of asparagine with glycine at the 21 position of the α-chain, and two arginines are added at the C-terminal of the β-chain.
- After injection into the subcutaneous tissue, the acid solution becomes neutralised and leads to micro-precipitate formation. These micro-precipitates release small amounts of insulin very slowly, which results in a relatively constant concentration and time profile over 24 hours without a pronounced peak. This profile allows for dosing once a day as a basal insulin level.
- It is generally taken at bedtime.

- As insulin glargine is presented in an acidic formulation, its ability to mix with other insulins is limited. This may also possibly account for increased injection pain.

Insulin Detemir

- Insulin detemir is soluble and has a neutral pH.
- It is an acylated derivative of human insulin with protracted action. When injected subcutaneously, insulin detemir binds to albumin via its fatty acid chain leading to a substantial reduction in the free insulin detemir concentration.
- By combining the basal soluble analogue insulin detemir and the rapid-acting analogue insulin aspart or lispro, it may be possible to more closely mimic near normal insulin profiles, with resulting improvement in glycaemic control compared with more conventional insulin therapy.

Insulin Degludec

- It forms soluble multihexamers at the injection site, from which monomers slowly separate and are absorbed.
- Has a long duration of action (>40 hours) and reduces variability in plasma concentration with once daily dosing.

Inhaled Insulin

- Inhaled human insulin powder was introduced in 2006 with much hope.
- Absorption of insulin was through the alveolar surface in the lungs.
- It was used with each meal along with single injection of long-acting insulin to provide basal levels of insulin.
- Side effects included cough, dry mouth, sore throat and shortness of breath, besides hypoglycaemia. It was not recommended in smokers, or those with asthma or chronic obstructive lung disease.
- Because of adverse effects, clinical efficacy similar to injectable insulin and cost issues, it was withdrawn in 2007.

Insulin Regimens

- Three treatment regimens will be described—i.e. conventional insulin therapy, multiple subcutaneous injections (MSI) and continuous subcutaneous insulin infusion (CSII).

Conventional Insulin Therapy

- In conventional insulin therapy, one or two injections a day of intermediate-acting insulin (lente) is administered, with or without the addition of small amounts of regular insulin.
- Insulin mixtures. Here, in addition to the intermediate-acting insulin, small doses of regular insulin are added to achieve better euglycaemic status.
- Split lente regimen. When the total daily insulin dose exceeds 50 or 60 units, or when diabetic state needs better control, the intermediate-acting insulin (lente) is given in two doses. Two-thirds of the total dose is given before breakfast (7–8 am) and the remaining one-third before dinner (7–8 pm).

Multiple Subcutaneous Injections (MSI)

- This involves administration of intermediate or long acting insulin in the evening as a single dose together with regular insulin prior to each meal. This regimen improves the overall control and may reduce the rate of development of long-term complications. A commonly used schedule is:
  - The total daily dose of insulin is calculated at 0.6–0.7 units/kg body weight.
  - The 25% of the calculated dose is given at bedtime in the form of an intermediate-acting insulin.
  - The 75% of the calculated dose is given in three divided doses as regular insulin (40% before breakfast, 30% before lunch and 30% before dinner).

Continuous Subcutaneous Insulin Infusion (CSII)

- This involves the use of a small battery-driven pump as a means of mimicking the physiological basal plus prandial pattern of insulin secretion. The insulin pump is worn externally and connected to a butterfly needle, which is inserted into the anterior abdominal wall.
- About 40% of the total daily dose is given at basal rate, the remainder being administered as preprandial boluses.
- The dangerous complication of this regimen is hypoglycaemia, especially nocturnal, which may be fatal.

Complications of Insulin Therapy

- Hypoglycaemia.
- Local allergic reactions at the injection site including local itching, erythematous and indurated lesions, and discrete subcutaneous nodules.
- Rarely, patients may develop systemic reactions, including generalised urticaria and anaphylactic reactions.

- Fat atrophy or fat hypertrophy may develop at the injection sites. Fat atrophy is usually due to impurities in the insulin preparation. Fat hypertrophy is attributed to the local lipogenic effects of the injected insulin.
- Formation of anti-insulin antibodies.

Pancreatic Transplantation

- Other options in patients with type 1 diabetes mellitus include pancreatic transplantation and islet cell transplantation.
- Both are capable of restoring normoglycaemia without exogenous insulin therapy and both have patient survival rates that are consistent with other organ transplantation procedures.

Q. Describe the assessment of metabolic control in diabetes.

- There are various methods of assessing blood glucose control in diabetic patients. Each method has its own advantages and disadvantages. The commonly employed methods are enumerated below.

Urinary Glucose

- Semi-quantitative measurements of urinary glucose and ketones can be obtained before breakfast and once or twice throughout the day. Patients should be instructed to void 30 minutes before obtaining urine for glucose determination ("double voiding"), particularly for the morning sample, so that the urinary glucose is more representative of the corresponding blood glucose. Regardless of this, it provides only a rough approximation of blood glucose levels. In addition, factors such as renal threshold, renal blood flow and urine volume greatly affect the meaning of urine glucose measurement (e.g.—a raised renal threshold for glucose may mask persistent hyperglycaemia).
- Periodic assessment of 24-hour urinary glucose excretion provides a better estimate of day-long control (less than 5 g/day indicates excellent control).

Blood Glucose

- Single random measurements of blood glucose levels are of limited value.
- Estimation of at least two blood glucose values (preprandial glucose and bedtime) must be done to assess the glycaemic control. The targets are:
  - Preprandial whole blood glucose 80–120 mg/dL (capillary plasma 90–130 mg/dL).
  - Peak post-prandial whole blood glucose (between 1 and 2 hours after meals) <160 mg/dL (capillary plasma 180 mg/dL).
- The best current method to assess glycaemic control is home- or self-monitoring of glucose. This requires the patient to assess his own blood glucose level daily and to make appropriate adjustments in insulin dosage. The measurements may be done using blood glucose test strips read either visually or with a reflectance meter.

Glycosylated Proteins

- Glycosylated haemoglobin (vide infra) can be measured which provides an excellent assessment of the overall state of glycaemic control during the preceding 3 months. In general, the goal is to get a value of less than 7%.
  - Some factors can influence HbA1c independent of glycaemia. The most common is any disease that alters red blood cell survival. Since glycation of haemoglobin occurs only as the erythrocyte circulates in serum, haemoglobin in the older erythrocytes is more glycosylated, haemoglobin in the reticulocyte is less. Total HbA1c reflects the mix of older and younger erythrocytes. Therefore, if the average life of red cells is abnormally short (as in, for example, haemolytic anaemia), then measured HbA1c will be lower, independent of glycaemia. Conversely, if the average age of circulating erythrocytes is older (as, for example, occurs if erythropoiesis is suddenly stopped in an aplastic anaemia), then the older red cell population would have higher HbA1c levels, regardless of glycaemia.
- Fructosamine assay measures glycation of all serum proteins. Since albumin accounts for most of the protein in blood, the fructosamine, for practical purposes, measures glycated albumin. As albumin has a turnover of about 2 weeks, fructosamine reflects glycaemia over this far shorter period.

Blood Lipids

- Concentrations of serum cholesterol, TG and HDL measured in the fasting state provide an index of overall metabolic control in diabetic patients.

Q. Discuss briefly glycosylated haemoglobin (HbA1c).

- When haemoglobin from a normal adult is passed through a chromatographic column, it separates into two major components:
  - Haemoglobin A (HbA) comprising 92–94% of the total haemoglobin.
  - Haemoglobin A1c (HbA1c) consisting of several, fast-moving components, comprising 6–8% of the total haemoglobin.

- The rate of synthesis of HbA1c depends on the exposure of the red cell to glucose, and hence, its level increases with hyperglycaemia.
- The percentage of glycosylated haemoglobin (HbA1c) gives an estimate of the diabetic control for the preceding 3 month period.
- The goal in general is to have HbA1c below 7% but for individual patients, it should be as close to normal (<6%) as possible without significant hypoglycaemia.

Q. Enumerate the complications of diabetes. How do you classify them?

Acute metabolic complications	Chronic (long-term) complications	

• Diabetic ketoacidosis (DKA)
• Hyperosmolar hyperglycaemic state (hyperosmolar non-ketotic diabetic coma)
• Hypoglycaemia
• Lactic acidosis
	Microvascular:
	• Diabetic retinopathy (non-proliferative and proliferative)
	• Cataract
	• Glaucoma
	• Neuropathy
	  • Sensory
	  • Motor
	  • Sensory motor
	  • Autonomic
	• Nephropathy
	  • Microalbuminuria
	  • Macroalbuminuria
	• Chronic kidney disease
		Macrovascular:
		• Coronary artery disease
		• Peripheral vascular disease
		• Cerebrovascular disease
		
		Others:
		• Gatroparesis
		• Dermatological complications

Q. Discuss the pathogenesis, clinical features, diagnosis, complications and management of diabetic ketoacidosis (DKA).

- DKA is a complication of type 1 DM. It is rare in type 2 DM.
- Precipitating factors of DKA include too little or no insulin intake, infections, severe stress (e.g. physical, emotional), and drugs (e.g. thiazides, corticosteroids).

Pathogenesis

- DKA results from insulin deficiency and glucagon excess.

Consequences of Insulin Deficiency

- Hyperglycaemia resulting in a hyperosmolar state which induces an osmotic diuresis leading to volume depletion and dehydration.
- Activation of lipolysis in adipose tissue results in release of increased amounts of free-fatty acids (FFA) into plasma, which are taken up by the liver. The fate of free-fatty acids in the liver is discussed below (see "consequences of glucagon excess").

Consequences of Glucagon Excess

- Accelerated hepatic gluconeogenesis and impaired peripheral utilisation of glucose, both resulting in severe hyperglycaemia. This hyperglycaemia induces an osmotic diuresis leading to volume depletion and dehydration.
- Activation of ketogenic process resulting in ketosis and metabolic acidosis. The mechanism is complex and involves the following sequences: the excess glucagon causes a resetting of the hepatic metabolism of free-fatty acids. This is achieved through an increased activity of the enzyme, carnitine acyltransferase. The result is that hepatic mitochondria convert free-fatty acids to ketone bodies which accumulate in the body fluids. The ketone bodies mainly include acetoacetic acid and β-hydroxybutyric acid, but to a minor amount, acetone also.
- The two strong acids, acetoacetic acid and β-hydroxybutyric acid, are responsible for the acidotic state. These acids dissociate completely, releasing hydrogen ions (H1) into the body fluids with a resultant fall in pH. The fall in pH is countered by the buffers, especially bicarbonate, which is used up.

Pathogenesis of Diabetic Ketoacidosis (DKA)—Summary

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Insulin deficiency                                          Glucagon excess

                              Hyperglycaemia

Activation of lipolysis      Osmotic diuresis          Activation of
(adipose tissue)                                       carnitine acyltransferase

Increased plasma             Volume depletion
FFA concentration            and dehydration

Increased hepatic                          +
FFA concentration

                    Accelerated ketogenesis
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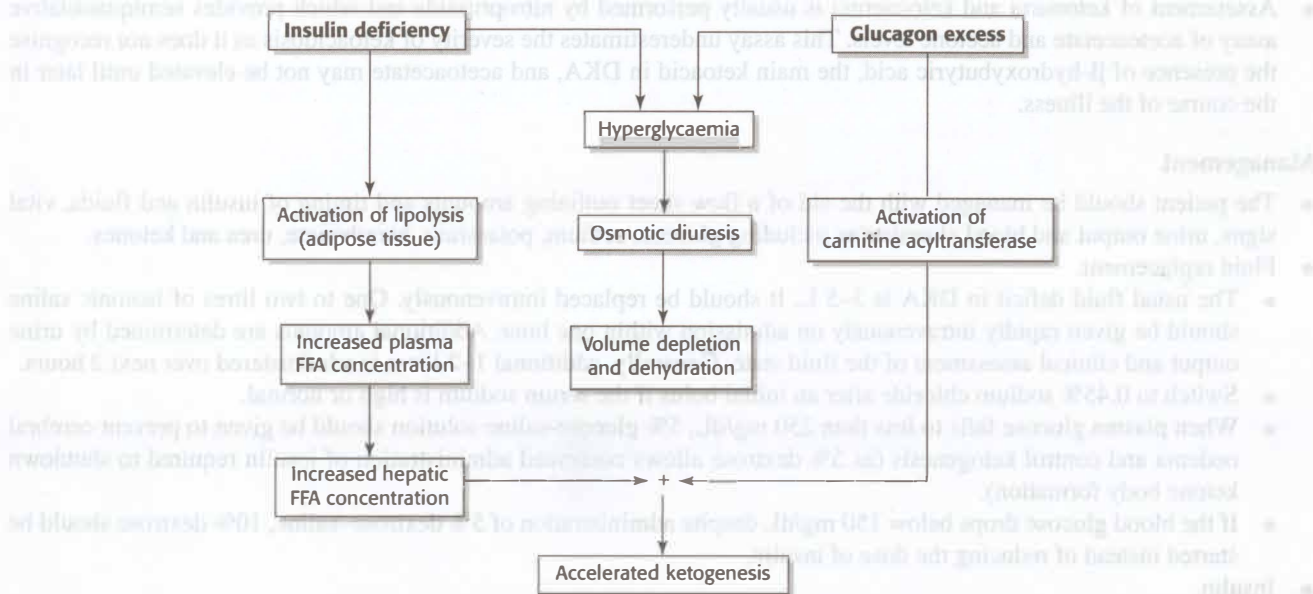
Clinical Features

- DKA begins with anorexia, nausea, vomiting and increased rate of urine formation.
- Abdominal pain is a dominant symptom.
- Altered consciousness or frank coma may occur in untreated cases.
- Kussmaul's breathing and a fruity odour to the breath due to acetone.
- Signs of volume depletion and dehydration are invariably present which may proceed to vascular collapse and renal failure.
- Body temperature is normal or low in uncomplicated DKA. Fever suggests infection.
- Leucocytosis is a feature of DKA per se, and may not indicate infection.

Complications

- Acute gastric dilatation or erosive gastritis, cerebral oedema, hyperkalaemia, hypokalaemia, hypoglycaemia, infections, insulin resistance, myocardial infarction, mucormycosis, ARDS and vascular thrombosis.
- Symptoms and signs of cerebral oedema include onset of headache, gradual deterioration in level of consciousness, seizures, sphincter incontinence, pupillary changes, papilloedema, bradycardia, elevation in blood pressure and respiratory arrest.

Investigations

- Urine examination shows glucose and ketones.
- Plasma glucose levels are raised, often markedly.
- Plasma ketone values are raised.
- Plasma potassium levels are normal or raised in the initial stages despite a total body deficit. This is due to metabolic acidosis which shifts potassium from intracellular compartment to extracellular compartment. The levels drop once the treatment is commenced.
- Plasma sodium levels are usually low, particularly if the patient has vomited repeatedly and continued to drink water.
- Serum phosphorus level may be high initially despite a total body deficit.
- Plasma bicarbonate levels are low, and a value less than 12 mmol/L indicates severe acidosis.
- The hydrogen ion (H1) concentration of the blood is raised and the pH low.
- Blood urea nitrogen (BUN) is usually elevated due to prerenal failure resulting from volume depletion.
- Serum amylase may be raised, especially in the presence of pancreatitis.
- Diagnosis criteria for DKA.
  - These are: blood glucose >250 mg/dL, arterial pH <7.3, serum bicarbonate <15 mEq/L and moderate degree of ketonaemia and/or ketonuria.

- The anion gap of >12 mEq/L is usually present in DKA patients.
- Assessment of ketonuria and ketonaemia is usually performed by nitroprusside test which provides semiquantitative assay of acetoacetate and acetone levels. This assay underestimates the severity of ketoacidosis as it does not recognise the presence of β-hydroxybutyric acid, the main ketoacid in DKA, and acetoacetate may not be elevated until later in the course of the illness.

Management

- The patient should be managed with the aid of a flow sheet outlining amounts and timing of insulin and fluids, vital signs, urine output and blood chemistries including glucose, sodium, potassium, bicarbonate, urea and ketones.
- Fluid replacement.
  - The usual fluid deficit in DKA is 3–5 L. It should be replaced intravenously. One to two litres of isotonic saline should be given rapidly intravenously on admission within one hour. Additional amounts are determined by urine output and clinical assessment of the fluid state. Generally, additional 1–2 litres is administered over next 2 hours.
  - Switch to 0.45% sodium chloride after an initial bolus if the serum sodium is high or normal.
  - When plasma glucose falls to less than 250 mg/dL, 5% glucose-saline solution should be given to prevent cerebral oedema and control ketogenesis (as 5% dextrose allows continued administration of insulin required to shutdown ketone body formation).
  - If the blood glucose drops below 150 mg/dL despite administration of 5% dextrose–saline, 10% dextrose should be started instead of reducing the dose of insulin.
- Insulin.
  - Insulin is generally started about an hour after IV fluid replacement is started.
  - DKA should be treated with regular insulin, preferably intravenously, may also be intramuscularly, but never subcutaneously. A reasonable goal is to maintain the plasma glucose level around 200 mg/dL.
  - Most patients can be treated by "low-dose" insulin schedules in which 8–10 units of regular insulin is infused intravenously each hour. At present a priming bolus dose is not recommended. Most patients respond to this schedule, but some may not, probably due to insulin resistance. They are identified by the persistence of acidosis despite several hours of treatment. For them, larger amounts of insulin should be given.
  - In patients with established diabetes, subcutaneous long-acting insulin (e.g. insulin glargine, detemir or ultralente) should be initiated at the dose that was used prior to the manifestation of DKA.
- Potassium replacement.
  - The initial potassium level is often high despite a total body deficit because of severe acidosis. With the initiation of therapy, reversal of acidosis and the action of insulin cause a shift of K⁺ into the intracellular space. This usually takes 3–4 hours, when plasma potassium levels drop. Potassium supplementation should commence at this stage.
  - If the admission potassium value is normal or low, potassium should be given early, to prevent hypokalaemia which can predispose to cardiac arrhythmias. In severe hypokalaemia, insulin is started only after potassium replacement is under way.
  - In view of the phosphate depletion, potassium should be administered initially as phosphate salt rather than as potassium chloride if initial phosphate is below 1 mg/dL.
- Bicarbonate therapy.
  - This is indicated only in patients with severe acidosis (pH ≤7.0), especially if hypotension or coma is present. Bicarbonate should be given as an infusion of isotonic of sodium bicarbonate (1.4%, i.e. 10 mL of 7.5% sodium bicarbonate is diluted with 50 mL of 5% dextrose or normal saline). The infusion should be stopped when the pH reaches 7.2.
- Prevention of cerebral oedema include avoidance of excessive hydration and rapid reduction of plasma osmolarity, a gradual decrease in serum glucose, and maintenance of serum glucose between 250 and 300 mg/dL until serum osmolality is normalised and mental status is improved. Mannitol infusion and mechanical ventilation are suggested for treatment of cerebral oedema.
- Initiate oral feeds when nausea and abdominal pain subside. Give a dose of regular insulin subcutaneously before stopping intravenous insulin.

Prognosis

- Major causes of death in DKA are myocardial infarction and infection, particularly pneumonia, and cerebral oedema in children.
- Poor prognostic signs at admission include hypotension, azotaemia, deep coma and associated illness.

Q. Briefly outline precipitating factors, clinical features, laboratory findings and management of hyperglycaemic hyperosmolar state (HHS).

Q. Describe hyperosmolar non-ketotic diabetic coma.

- The terms "hyperglycaemic hyperosmolar non-ketotic coma", "hyperosmolar non-ketotic diabetic coma" and "hyperglycaemic hyperosmolar non-ketotic state" have been replaced with the term hyperglycaemic hyperosmolar state (HHS) as coma may not be present in all cases, and variable degree of ketosis may be present as determined by the nitroprusside method.
- Usually a complication of type 2 diabetes.
- This is a syndrome characterised by extreme dehydration resulting from a sustained hyperglycaemic diuresis under circumstances in which the patient is unable to drink sufficient water. The biochemical hallmark of the syndrome is extreme hyperglycaemia in the absence of significant ketoacidosis.
- The syndrome has a high mortality rate of more than 50%.

Precipitating Factors

- Infections.
- Cerebrovascular accidents.
- Peritoneal dialysis and haemodialysis.
- Tube feeding of high-protein formulas.
- Parenteral nutrition.
- Osmotic agents like mannitol.
- Steroids, immunosuppressive agents, phenytoin and diuretics.

Clinical Features

- Onset is usually more insidious as compared to DKA.
- Signs of volume depletion and extreme dehydration are invariably present.
- Central nervous system manifestations include alteration in the level of consciousness ranging from clouded sensorium to coma, convulsions (sometimes Jacksonian in type) and transient hemiplegia.
- Infections, particularly pneumonia and gram-negative sepsis are very common.
- Bleeding and acute pancreatitis may accompany the illness.

Laboratory Findings

- Plasma glucose is markedly elevated, usually around 1000 mg/dL (range 600–2400 mg/dL).
- Serum osmolality is markedly raised.
- Prerenal azotaemia with elevation of BUN and creatinine.
- A mild metabolic acidosis with marginal decrease in plasma bicarbonate (about 20 mmol/L) is present. Marked decrease in plasma bicarbonate (<10 mmol/L) indicates lactic acidosis.
- Diagnostic criteria for HHS include plasma glucose more than 600 mg/dL, osmolality more than 330 mOsm/kg and absence of severe ketoacidosis. The blood pH is usually more than 7.3 with bicarbonate more than 18 mEq/L. Approximately 50% of the patients with HHS have an increased anion gap metabolic acidosis as a result of concomitant ketoacidosis and elevated lactate levels.

Management

- Fluid replacement. The average fluid deficit is about 10 L that should be corrected intravenously. Initially 2–3 L of isotonic (0.9%) saline should be given over 1–2 hours. Subsequently, half-strength (0.45%) saline should be used. Once the plasma glucose approaches 300 mg/dL, 5% dextrose–saline solution should be used.
- Insulin. Regular insulin should be given as a low-dose intravenous infusion, as for DKA. It should be started after initial bolus of saline has been given. The goal is to keep the plasma glucose around 200 mg/dL. Rapid reductions in glucose levels are undesirable as this can lead to large shifts in water and sodium status resulting from rapid changes in serum osmolality.
- Potassium supplementation is required early, as for DKA.
- Lactic acidosis should be treated with intravenous sodium bicarbonate.
- Infections should be treated with antibiotics.
- Anticoagulants should be given to prevent thrombosis.

Q. How will you differentiate between diabetic ketoacidosis (DKA) and hyperglycaemic hyperosmolar state (HHS)?

Clinical and Laboratory Features

Features	DKA	HHS
• Type of diabetes	Type 1 or 2	Type 2
• Evolution	Over hours	Over days
• Acetone odour on breath	Yes	No
• Kussmaul's respiration	Yes	No
• Abdominal pain/tenderness	Yes	No
• Blood glucose	>250 mg/dL	>600 mg/dL
• Serum sodium	Normal or low	Usually high
• Blood/urine ketones	+ + + +	Negative or trace
• Blood pH	<7.3	>7.3
• Serum bicarbonate	<18 mEq/L	>18 mEq/L
• Serum osmolality	Variable	>330 mOsm/kg
• Mortality	5–10%	20–30%

Q. Discuss the pathogenesis, clinical features and management of hypoglycaemia.

- Hypoglycaemia is a dangerous complication, and in the short run, more serious than hyperglycaemia. Prolonged hypoglycaemia may cause permanent brain damage. Hypoglycaemia commonly complicates therapy with insulin and oral antidiabetic drugs. Less commonly, hypoglycaemia occurs in non-diabetic subjects (due to drugs like pentamidine, didanosine, oral antidiabetic agents; alcohol intoxication; insulin-secreting tumours—insulinoma; gastric bypass).

Pathogenesis

- Protection against hypoglycaemia is normally provided by two mechanisms as plasma glucose concentration falls:
  - Cessation of insulin release.
  - Secretion of counter-regulatory hormones.
- The four counter-regulatory hormones are glucagon, catecholamines (adrenaline and noradrenaline), cortisol and GH. They counter hypoglycaemia by increasing hepatic glucose production and decreasing glucose utilisation by non-hepatic tissues. Glucagon is the primary counter-regulatory hormone, while catecholamines serve as the major backup. Cortisol and GH do not function acutely, but come into play with sustained hypoglycaemia.
- Diabetic patients are vulnerable to hypoglycaemia due to two reasons:
  - Insulin excess.
  - Counter-regulatory failure. In the early stages itself, type 1 DM patients lose the capacity to increase glucagon release in response to hypoglycaemia. Many patients, subsequently, also lose the capacity to release catecholamines in response to hypoglycaemia, as a result of diabetic autonomic neuropathy.

Clinical Features

- Hypoglycaemia usually follows a missed meal, too much insulin or unexpected exercise.
- Symptoms due to hypoglycaemia usually occur with a plasma glucose level of 60 mg/dL in non-diabetic persons.
- Poorly controlled diabetic patients develop symptoms at higher levels (80 mg/dL), while well-controlled diabetic patients develop symptoms at lower levels.
- Symptoms of hypoglycaemia fall into two main categories:
  - Adrenergic symptoms induced by excessive secretion of adrenaline include sweating, tremor, tachycardia, anxiety and hunger.
  - Central nervous system dysfunction causes dizziness, headache, clouding of vision, blunted mental acuity, loss of fine motor skill, confusion, abnormal behaviour, convulsions and loss of consciousness.
- When hypoglycaemia is of rapid onset (e.g. insulin reactions), adrenergic symptoms predominate. When hypoglycaemia is of gradual onset, manifestations of central nervous system predominate.
- In long-standing diabetics, adrenergic symptoms may not manifest due to severe neuropathy. Consequently, central nervous system manifestations may predominate.

- Indications of daytime hypoglycaemic episodes are sweating, nervousness, tremor and hunger.
- Indications of nocturnal hypoglycaemic episodes during sleep include night sweats, unpleasant dreams and early morning headache. Frequently, nocturnal hypoglycaemic is asymptomatic.
- Hypoglycaemia due to overdosage with unmodified insulin occurs at the time when the insulin has its maximum effect. With the standard twice daily regimen, it is likely to occur in the late morning or early evening.
- Hypoglycaemia from excessive depot-insulin given before breakfast usually occurs in the late afternoon. Depot-insulin given before the evening meal causes hypoglycaemia through the night and in the early hours of the morning.
- Hypoglycaemia occurring with long-acting sulphonylureas may be prolonged, refractory and dangerous.

Management

- Oral carbohydrate: If hypoglycaemia is recognised early, it may be corrected by ingestion of carbohydrate, preferably in an easily absorbable form.
- Intravenous dextrose: This is indicated in serious hypoglycaemia, when mental function is impaired, and prolonged hypoglycaemia is anticipated (e.g. with depot-insulin and oral sulphonylureas like chlorpropamide). 50 mL of 50% dextrose should be given initially, followed by infusion of 5–10% dextrose. Oral carbohydrate should be administered as soon as the patient is able to eat.
- Glucagon: Severe hypoglycaemia may be treated with glucagon 1 mg subcutaneously or intramuscularly, and repeated if necessary after 10 minutes. Glucagon acts by stimulation of hepatic glycogenolysis. It may not be effective in severe and prolonged hypoglycaemia due to depot-insulins. It should not be used to treat hypoglycaemia induced by oral anti-diabetic drugs.
- Octreotide is effective for patients who develop recurrent hypoglycaemia following dextrose infusion.
- Other measures: These are aimed at prevention of recurrence. They include adjustments in the dosage of oral hypoglycaemic drugs, changing the timing of insulin injections, adjustments in diet and physical activity, etc.

Q. Describe Somagyi phenomenon and dawn phenomenon.

The Somagyi Phenomenon

- The Somagyi phenomenon (post-hypoglycaemic hyperglycaemia) refers to rebound hyperglycaemia following an episode of hypoglycaemia, due to counter-regulatory hormone release. The rebound hyperglycaemia manifests as morning fasting hyperglycaemia, in response to unrecognised nocturnal hypoglycaemia.
- The significance of the Somagyi phenomenon is that the correction of the morning hyperglycaemia depends on reducing, and not increasing the evening dose of intermediate-acting insulin.

Clues to the Presence of Somagyi Phenomenon

- The classical clinical picture is one of worsening diabetic control in the presence of increasing insulin doses and is manifested especially by fasting hyperglycaemia.
- Excessive hunger and weight gain occurring in the context of worsening hyperglycaemia.
- Subtle clinical signs of nocturnal hypoglycaemia, such as mild nocturnal sweating, morning headaches and hypothermia.
- Wide fluctuations in the plasma glucose and urine glucose occurring over short time intervals, and not related to meals.
- The Somagyi phenomenon can be confirmed by documenting hypoglycaemia at 3 am and hyperglycaemia in the morning (fasting state).
- The ultimate criterion for the diagnosis of Somagyi phenomenon is improvement in diabetic control after a decrease in the insulin dose.

The Dawn Phenomenon

- This phenomenon is closely related to the Somagyi phenomenon in that there is fasting hyperglycaemia, but no hypoglycaemia during the night.
- The mechanism of the dawn phenomenon is thought to be nocturnal surge of GH release or increased clearance of insulin in the mornings.
- The dawn phenomenon can be confirmed and differentiated from the Somagyi phenomenon by documenting hyperglycaemia at 3 am and in the morning (fasting state).
- The significance of the dawn phenomenon is that the correction of the fasting hyperglycaemia depends on increasing and not decreasing the insulin.

Q. Enumerate the differences in coma due to hypoglycaemia and ketoacidosis in type 1 DM.

Feature	Hypoglycaemic coma	Coma with ketosis
• History	No food; too much insulin; unaccus-tomed exercise	Too little or no insulin; an infection; digestive disturbance
• Onset	In good previous health; related to last insulin injection	Ill-health for several days
• Symptoms	Of hypoglycaemia	Of glycosuria and dehydration; abdominal pain and vomiting
• Signs	Moist skin and tongue Full pulse Normal or raised blood pressure Shallow or normal breathing Brisk reflexes	Dry skin and tongue Weak pulse Low blood pressure Kussmaul's breathing; acetone smell
• Urine	No ketonuria No glycosuria	Ketonuria Glycosuria
• Blood	Hypoglycaemia Normal plasma bicarbonate	Hyperglycaemia Reduced plasma bicarbonate

Q. How does lactic acidosis occur in a diabetic patient? Briefly outline the clinical setting, manifestations, diagnosis and management of lactic acidosis.

- Lactic acidosis occurs when lactic acid is produced at accelerated rates due to anaerobic metabolism in skeletal muscles and other tissues. In a diabetic it usually occurs as a complication of treatment with biguanides, usually with phenformin (not available now) and rarely with metformin. These drugs inhibit hepatic gluconeogenesis from lactate, pyruvate and alanine.
- Clinical manifestations include nausea, vomiting, restlessness, Kussmaul's breathing and alteration in the level of consciousness ranging from stupor to coma.
- Diagnosis is confirmed by a low arterial pH (<7.2), increased anion gap, decreased plasma bicarbonate and a high concentration (>5.0 mmol/L) of lactic acid in the blood.
- Lactic acidosis should be treated with intravenous sodium bicarbonate to raise the plasma pH to above 7.0. Intravenous insulin and glucose are also required.

Q. What are the cardiovascular complications of diabetes?

- The main cardiovascular complications of diabetes are accelerated atherosclerosis, and increased platelet adhesiveness, possibly due to enhanced thromboxane A_2 synthesis and decreased prostacyclin synthesis.
- The atherosclerotic lesions can manifest in a variety of ways:
  - Intermittent claudication, gangrene and impotence.
  - Coronary artery disease leading to ischaemic heart disease, especially silent myocardial infarctions.
  - Cerebrovascular accidents.
- Another effect is development of diabetic cardiomyopathy that is possibly related to direct effects of diabetes on the myocardium. It is not due to hypertension, coronary artery disease or any other known cardiac disease. The patient may have diastolic dysfunction, systolic dysfunction or both.

Q. What are the stages in the development of diabetic nephropathy?

Q. Describe Kimmelstiel–Wilson lesions.

- Diabetic nephropathy is a leading cause of death and disability in diabetes. It is more common in type 1 DM than type 2 DM.

Pathology

- Diabetic nephropathy involves two distinct pathologic patterns that may or may not coexist.

- In the diffuse form that is more common, there is widening of the glomerular basement membrane together with generalised mesangial thickening.
- In the nodular form, large accumulations of PAS-positive material are deposited at the periphery of glomerular tufts, the Kimmelstiel–Wilson lesion.
- In addition, there may be hyalinisation of afferent and efferent arterioles, "drops" in Bowman's capsule, fibrin caps and occlusion of glomeruli. Deposition of albumin and other proteins occurs in both glomeruli and tubules.

Clinical Features

- The earliest stage is characterised by nephromegaly (enlargement of kidneys) and "hyperfunction" or "hyperfiltration" (i.e. increased glomerular filtration).
- The next stage is characterised by microproteinuria (micro-albuminuria) with the urinary excretion of albumin in the range of 30–300 mg/day. Normal persons excrete less than 30 mg/day. At this stage the disease is probably reversible. Microalbuminuria is also a well-established marker of increased cardiovascular disease risk. Because of the long duration of abnormal glucose metabolism that often precedes diagnosis, patients with type 2 diabetes are more likely to have microalbuminuria (or overt nephropathy) at diagnosis. Thus, patients with type 2 diabetes should be screened at the time of diagnosis for the presence of microalbuminuria.
- The next stage is characterised by macroproteinuria (macro-albuminuria) with the urinary excretion of albumin more than 300 mg/day. From this stage, the disease is irreversible, and a steady decline in glomerular filtration rate occurs at a rate of about 1 mL/minute/month. The stage of macroproteinuria may progress to include all the classic features of the nephrotic syndrome.
- With further progression, azotaemia develops and progression to renal failure and uraemia is inevitable.

Diagnosis of Microalbuminuria.

- Screening for microalbuminuria can be accomplished in a variety of ways.
  - Measurement of albumin-to-creatinine ratio on a spot urine test. This is obtained most easily and collection errors occur less frequently. A ratio of more than 30 mg albumin/g creatinine is considered elevated on a spot urine test.
  - Albumin from a 24-hour urine collection (urinary albumin >30 mg/24 hours is diagnostic).
- Transient elevations of microalbuminuria can be caused by exercise, urinary tract infections, hyperglycaemia, febrile illness, severe hypertension or heart failure.

Management

- Stop smoking and control dyslipidaemia.
- Meticulous control of diabetes can reverse microproteinuria in some patients.
- In addition, angiotensin converting enzyme inhibitors can retard the progression of nephropathy at this stage.
- Aggressive control of hypertension is mandatory as high blood pressure can accelerate nephropathy.
  - The blood pressure should be decreased to less than 140/90 mmHg.
  - ACE inhibitors and angiotensin-receptor blockers have proved beneficial in patients with diabetic renal disease and are considered preferred therapy in patients with hypertension and diabetes. These agents can be used if creatinine is less than 3 mg/dL.
  - Aldosterone inhibitor when added to an ACE inhibitor conveys a significant decrease in proteinuria although this is associated with an increased risk of hyperkalaemia,
  - Other agents that can be used include thiazide diuretics, calcium channel blockers, β-blockers and α-blockers.
- Low-protein diets (0.8 g/kg/day) may be beneficial, as there is some evidence suggesting that high-protein diets can accelerate glomerulosclerosis.
- Once the azotaemic phase is reached the management is similar to other forms of chronic renal failure.

Q. Discuss briefly diabetic retinopathy.

- A 1% decrease in glycated haemoglobin roughly equates to a decreased risk of retinopathy by 40%.
- Puberty and pregnancy are risk factors for diabetic retinopathy in people with type 1 diabetes.
- Implicated pathogenetic mechanisms include accumulation of sorbitol and advanced glycation end-products, oxidative stress, protein kinase C activation, inflammation, and up regulation of the renin–angiotensin system and vascular endothelial growth factor.
- Retinopathic lesions are divided into two large categories, simple (background or non-proliferative) and proliferative.

Lesions of Diabetic Retinopathy

Simple (background)	Proliferative
• Increased capillary permeability	• New vessels
• Capillary closure and dilatation	• Scar (retinitis proliferans)
• Microaneurysms	• Vitreal haemorrhage
• Arteriovenous shunts	• Retinal detachment
• Dilated veins	
• Haemorrhages (dot and blot)	
• Cotton-wool spots	
• Hard exudates	

- Treatment involves tight control of diabetes and hypertension.
- Diabetic retinopathy is treated by photocoagulation.
- Pars plana vitrectomy is utilised for the treatment of non-resolving vitreal haemorrhage and retinal detachment.

Q. Discuss the classification, clinical manifestations and management of diabetic neuropathy.

Classification

Symmetric distal polyneuropathy	Asymmetric neuropathy
• Distal symmetrical sensorimotor polyneuropathy	• Cranial mononeuropathy and mononeuropathy multiplex
• Painful autonomic neuropathy	• Peripheral mononeuropathy and mononeuropathy multiplex
• Painful distal neuropathy with weight loss ("diabetic cachexia")	• Median neuropathy at wrist
• Insulin neuritis	• Ulnar neuropathy at elbow
• Polyneuropathy after ketoacidosis	• Peroneal neuropathy at fibular head
• Polyneuropathy with glucose impairment	• Radiculoplexoneuropathies
• Chronic inflammatory demyelinating polyneuropathy with diabetes mellitus	• Lumbosacral
	• Thoracic
	• Cervical
	• Neuromuscular syndromes (e.g. diabetic amytrophy)
	Autonomic neuropathy

- Symmetric neuropathies are due to "metabolic" abnormalities of the neurons of Schwann cells, whereas the asymmetric neuropathies are due to vascular occlusion and ischaemia.

Distal Symmetric Sensorimotor Polyneuropathy

- This form of diabetic neuropathy can be divided into two types:
  - A relatively asymptomatic form that is diffuse, distal, usually occurring in the lower extremities with a stocking type of distribution. There is numbness, tingling or pins-and-needles sensation often worse at night. This type is generally progressive and irreversible.
  - A painful form presenting with burning or dull aching sensation or excruciating, lancinating pain. The pain is often worse at night and partially relieved by movement. Hyperaesthesia may be marked.
- The characteristic early physical findings in both forms are loss of vibration sense and deep tendon reflexes (especially ankle jerk). With progression there may be involvement of other sensations like joint position, touch, pain and temperature, later leading to weakness and wasting of muscles.

Asymmetric Neuropathy

- Diabetic mononeuropathies of the cranial nerves usually involve IIIrd, VIth or IVth cranial nerve in order of frequency. Third nerve involvement is characteristically pupil-sparing.
- Mononeuropathies of peripheral nerves manifest as carpal tunnel syndrome, foot drop or wrist drop.
- Radiculopathy is a sensory syndrome in which dysaesthesias and painful hyperaesthesia occur in the anatomic distribution of one or more spinal nerves.

- Diabetic amyotrophy (diabetic proximal neuropathy) is characterised by atrophy and weakness of the muscles of thigh (especially quadriceps) and pelvic girdle. This may be associated with anorexia and depression.

Autonomic Neuropathy

- Denervation of sympathetic and parasympathetic systems result in loss of awareness of hypoglycaemia.
- The common manifestations of autonomic neuropathy in diabetes are given in the box.

Manifestations of diabetic autonomic neuropathy	
• Cardiovascular	Postural hypotension, resting tachycardia, absence of sinus arrhythmia, abnormal Valsalva response, sudden cardiac death
• Gastrointestinal	Oesophageal dysmotility, dysphagia, gastroparesis, nocturnal and post-prandial diarrhoea, constipation, anal incontinence
• Genitourinary	Vesicopathy, incontinence, impotence, retrograde ejaculation
• Secretomotor	Gustatory sweating, nocturnal sweats without hypoglycaemia, anhidrosis
• Vasomotor	Dependent pedal oedema
• Pupillary	Decreased pupil size, resistance to mydriatics

Diagnosis

- Clinical examination including assessment of muscle power, sensations of pinprick, joint position, touch and temperature. Vibration test should be done by tuning fork of a 128 Hz.
- Autonomic function tests based on blood pressure and heart rate response to a series of manoeuvres.
- Nerve conduction studies.
  - Motor nerve conduction, F response and sensory nerve conduction studies are important methods of documentation and follow-up of nerve functions.
  - Motor nerve conduction studies are affected in a small subset (large fibre neuropathies).
  - Entrapment neuropathies result in unilateral nerve conduction velocity (NCV) changes, especially across the entrapped segment of the nerve.
  - The commonest abnormality is reduction in the amplitude of motor or sensory action potentials because of axonopathy.
  - Pronounced slowing of NCV suggests demyelinating neuropathy, which is rarely associated with diabetes; therefore, pronounced slowing of NCV in a diabetic patient should prompt investigations for an alternative diagnosis.

Management

- Mononeuropathies and radiculopathies are usually self-limiting and do not require any specific therapy.
- Pain of diabetic neuropathy may be treated with non-steroidal anti-inflammatory drugs, phenytoin, carbamazepine, amitriptyline, imipramine, gabapentin or pregabalin. Duloxetine, a potent dual reuptake inhibitor of serotonin and noradrenaline has been found to be useful in refractory cases.
- Diabetic diarrhoea often responds to diphenoxylate, loperamide or tetracyclines.
- Orthostatic hypotension often responds to sleeping with the head of the bed elevated, avoidance of sudden assumption of the upright position, full-length elastic stockings and increased salt intake. Rarely, fludrocortisone is required.
- Gastroparesis may be treated with frequent small meals and prokinetic agents.
- Erectile dysfunction may be treated with psychological counselling, sildenafil, vardenafil, tadalafil, prostaglandin E_1 injection, device or prosthesis.

Specific Treatment to Reverse Neuropathy

- Aldolase reductase inhibitors (e.g. epalrestat) reduce the flux of glucose through polyol pathways, inhibiting accumulation of sorbitol and fructose, and preventing reduction of redox potential. However, their use has not been found to be effective.
- α-Lipoic acid is a natural cofactor of dehydrogenase complex and is a redox modulating agent. It has been shown to be effective in ameliorating both somatic and autonomic diabetic neuropathies.
- Carnitine may be useful in some patients.
- Methylcobalamin has also been shown to provide some benefit in patients with diabetic neuropathy.

Q. What are the dermatological complications of diabetes?

- Skin infections such as carbuncles and furuncles.
- Diabetic ulcers (due to peripheral neuropathy and ischaemia)

- Vaginal candidiasis.
- Necrobiosis lipoidica diabeticorum.
- Diabetic dermopathy (shin spots).
- Acanthosis nigrans.
- Xanthomatoses secondary to hyperlipoproteinaemia.
- In type 1 patients, tight, scleroderma-like waxy skin over the dorsum of the hands in conjunction with joint contractures has been observed.

Q. What is gestational diabetes mellitus (GDM)? How will you diagnose it?

Q. Discuss the significance and management of gestational diabetes mellitus.

Q. Describe the O'Sullivan criteria for the diagnosis of gestational diabetes mellitus.

Q. Describe Carpenter and Coustan criteria for the diagnosis of gestational diabetes mellitus.

- Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance that begins or is first recognised during pregnancy. The definition applies whether insulin or only diet modification is used for treatment and whether or not the condition persists after pregnancy. It does not exclude the possibility that unrecognised glucose intolerance may have antedated or begun concomitantly with the pregnancy.
- However, it has recently been recommended that high-risk women found to have diabetes at their initial prenatal visit using standard criteria receive a diagnosis of overt, not gestational, diabetes. Further, women with GDM should be screened for diabetes 6–12 weeks post-partum.
- The importance of proper diagnosis can be appreciated as GDM is known to cause increased foetal loss (two to three times greater risk than general population) and congenital malformations like foetal macrosomy.
- Further, females with GDM are at increased risk for the development of diabetes after pregnancy.
- Offsprings of females with GDM are at increased risk of obesity and diabetes.
- The diagnosis of GDM is based on an oral glucose tolerance test (OGTT) done at 24–28 weeks of gestation in women with moderate to high risk. It is not required in women with low risk of GDM that is defined as presence of all of the following.

- Age <25 years
- Weight normal before pregnancy
- Member of an ethnic group with a low prevalence of diabetes
- No known diabetes in first-degree relatives
- No history of abnormal glucose tolerance
- No history of poor obstetrical outcome

- 100 g OGTT is recommended at present. A larger than usual glucose load (75 g) is advocated as there is an increased turnover of glucose in pregnant state. Hundred grams of glucose is dissolved in 300–400 mL of water and consumed over 5 minutes.
- The first criteria for diagnosing GDM were given by O'Sullivan and were based on whole blood glucose levels. However, as the levels of glucose may vary in whole blood due to uptake by red blood cells, Carpenter and Coustan have given new values based on plasma glucose levels.

Criteria for Diagnosis of GDM

Time (hour)	Upper limit of normal values (mg/dL)	
	Whole blood (O'Sullivan)	Plasma (Carpenter & Coustan)
0 (Fasting)	85	95
1	160	180
2	140	155
3	125	140

(Two or more of these values must be abnormal).

- Management. Oral antidiabetic drugs are contraindicated in GDM. These pregnant diabetics should be managed meticulously with insulin.

Q. Give a brief account of metabolic syndrome.

Q. Discuss briefly clinical diagnosis, risks and treatment of insulin resistance syndrome (syndrome X).

- Metabolic syndrome (previously known as syndrome X or insulin resistance syndrome) refers to the clustering of risk factors for cardiovascular and type 2 diabetes mellitus and includes abdominal obesity, hyperglycaemia, dyslipidaemia (high TGs, low HDL) and elevated blood pressure.
- The clinical relevance of metabolic syndrome is that it identifies people who are at increased long-term risk of cardiovascular disease and type 2 diabetes, thus providing an opportunity for preventive lifestyle interventions.
- The underlying defect in this syndrome is insulin resistance.
    - Defined as inability of insulin to produce its numerous actions, in spite of unimpaired secretion from the β cells.
    - Except in a few rare cases involving antibodies against insulin receptor or mutations in the insulin receptor gene, insulin resistance of metabolic syndrome results from impairments in cellular events distal to the interaction between insulin and its surface receptor.
    - Metabolic abnormalities result from interaction between effects of insulin resistance located primarily in the muscle and adipose tissue, and adverse impact of compensatory hyperinsulinaemia on tissues that remain normally insulin sensitive.

Clinical Diagnosis

- Presence of at least three of the following:
    - Abdominal obesity (waist circumference >80 cm in females and >90 cm in males).
    - elevated TG levels (≥150 mg/dL).
    - reduced HDL-cholesterol level (<40 mg/dL in males and <50 mg/dL in females).
    - elevated blood pressure (systolic ≥130 mmHg or diastolic ≥85 mmHg).
    - elevated fasting plasma glucose level, i.e. impaired fasting glucose (100–125 mg/dL).
- People receiving medical treatment for dyslipidaemia or hypertension, and those with isolated systolic or diastolic hypertension are included in the above criteria.

Associated Risks

- Cardiovascular diseases	- Sleep-disordered breathing
- Type 2 diabetes mellitus	- Chronic kidney disease
- Polycystic ovary syndrome	- Erectile dysfunction
- Non-alcoholic fatty liver disease	- Hepatocellular and intrahepatic cholangiocarcinoma
- Hyperuricaemia and gout	

Treatment

- There is currently no sound evidence showing that the treatment of insulin resistance reduces mortality and morbidity in these patients. Nevertheless, treatment of insulin resistance involves lifestyle changes.
- Components of therapy include:
    - Exercise
    - Hypocaloric diet.
    - Weight reduction.
    - Diet high in fibres.
- Control of diabetes, hypertension and lipid abnormalities by various drugs.
- In the absence of diabetes, hypoglycaemic drugs (e.g. metformin, acarbose) are not recommended to control insulin resistance.

Q. Write a short note on lipodystrophy.

- Lipodystrophy implies redistribution of fat tissue. Lipoatrophy refers to partial or complete decrease of adipose tissue. The terms lipoatrophy and lipodystrophy are used interchangeably in clinical practice.

- Lipodystrophies include three main groups: generalised, partial (extensive, but not generalised) and localised (limited to isolated areas).

Classification of Lipodystrophies

Inherited	Acquired

• Congenital generalised lipodystrophy
• Familial partial lipodystrophy
• Mandibuloacral dysplasia
	• Acquired generalised lipodystrophy
	• Acquired partial lipodystrophy
	• Lipodystrophy in HIV-infected patients
	• Localised lipodystrophy
	  • Drugs (injectable drugs like insulin, glucocorticoids, methotrexate)
	  • Pressure, trauma
	  • Panniculitis
	  • Idiopathic

Clinical Findings in Generalised Lipodystrophy

• Lipodystrophy	• Acanthosis nigricans
• Metabolic disease	• Hepatic disease (steatosis, cirrhosis)
• Insulin resistance	• Proteinuria
• Hyperglycaemia	• Hypertrichosis, hirsutism, polycystic ovarian syndrome
• Hypertriglyceridaemia	• Muscular hypertrophy
• Lactic acidosis	• Mental retardation

Treatment

- Low fat diet.
- Treatment of diabetes, hypertriglyceridaemia.
- Metreleptin (a leptin analogue) in conjunction with diet to treat leptin deficiency in patients with congenital generalised or acquired generalised lipodystrophy. It is not approved for treatment of HIV-associated lipodystrophy.

HIV-Associated Lipodystrophy

- Peripheral lipoatrophy, central fat accumulation and lipomatosis.
- Related to use of protease inhibitors and nucleoside reverse transcriptase inhibitors; may occur in treatment—naïve patients also.
- Affected patients frequently show associated metabolic features (e.g. reduced HDL-cholesterol, hypertriglyceridaemia, insulin resistance, type 2 diabetes mellitus and lactic acidosis).
- Usually starts in the first 6–12 months after beginning therapy.
- Commonly encountered patterns of lipodystrophy include.
  - Generalised or localised lipoatrophy of face, extremities and buttocks.
  - Lipohypertrophy with generalised or local fat deposition involving abdomen, breasts, and supraclavicular and dorsocervical regions (buffalo hump).
  - A mixed pattern with central adiposity and peripheral lipoatrophy.
- No specific treatment has been found to be useful although several drugs like metformin and pioglitazone have been tried. Switching from an NRTI (i.e, stavudine or zidovudine) to an alternative agent such as abacavir or tenofovir may be tried.

Q. Discuss the structure of lipoproteins and their transport in body.

Q. Discuss hyperlipidaemias, their causes and management.

- Cholesterol and triglyceride (TG) constitute the lipid particles in the body. These lipids are transported in the blood in complexes known as lipoproteins.

- Plasma lipoproteins are composed of a core of TG and cholesterol ester, enveloped by a surface coat of phospholipids, unesterified cholesterol and special proteins called apolipoproteins. Apolipoproteins (apo) such as apoB, apoC and apoE, coat lipoprotein particles and serve a number of functions including transport of lipids in the blood and recognition of lipoprotein particles by enzymes that process or remove lipids from the lipoprotein particles.
- The five main classes of lipoproteins are:
  - Chylomicrons.
  - Very low density lipoprotein (VLDL).
  - Intermediate density lipoprotein (IDL).
  - Low-density lipoprotein (LDL).
  - High-density lipoprotein (HDL).
- Lipoprotein(a) [Lp(a)] is another lipoprotein particle that in structure is very similar to LDL with the addition of apolipoprotein(a). Lp(a) links lipid metabolism with blood coagulation and is thought to be both atherogenic and thrombogenic.
- Small, dense LDL particles containing more cholesterol ester are considered to be more atherogenic than LDL particles.

Lipid Transport in Body

- There are three main pathways responsible for the generation and transport of lipids within the body.

Exogenous (dietary) Lipid Pathway

- Following digestion and absorption of dietary fat, TG and cholesterol are packaged to form chylomicrons in the epithelial cells of the intestines.
- Chylomicrons are the largest lipoprotein and are rich in TG.
- They are transported in the blood to tissues such as skeletal muscle, fat and liver.
- Lipoprotein lipase (LPL) hydrolyses TG in the chylomicrons into free-fatty acids that are either oxidised by the muscle cells to generate energy, stored in adipose tissue, oxidised in the liver or used in hepatic VLDL synthesis.

Endogenous Pathway

- The endogenous pathway involves the liver synthesising lipoproteins.
- TGs and cholesterol ester are generated by the liver and packaged into VLDL particles and then released into the circulation.
- The TG component of VLDL undergoes hydrolysis by capillary LPL to provide fatty acids to adipose and muscle tissue. The remaining lipid portion is called intermediate density lipoprotein (IDL). IDL is then converted to LDL by enzymatic action of hepatic lipase or is taken up by the liver via the LDL receptor.
- LDL particles carry the majority of the cholesterol in the blood supplying cholesterol to the cells.
- LDL receptors in peripheral cells or liver bind with LDL and clear it from the blood.
- Peripheral cells utilise LDL cholesterol for cell membrane structure and also the production of hormones.
- LDL is an atherogenic lipoprotein particle.
- Plasma LDL concentration is regulated by:
  - Altering the synthesis of hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase that controls the rate of cholesterol synthesis.
  - Suppressing the synthesis of new LDL receptors in the cells.

Reverse Cholesterol Transport

- Reverse cholesterol transport refers to the process by which cholesterol is removed from the tissues and returned to the liver.
- HDL is the key lipoprotein involved in reverse cholesterol transport. It is synthesised and catabolised in the liver and intestines.
- It facilitates the transfer of cholesterol from atherogenic lipoproteins and peripheral tissues to the liver. A circulating enzyme called lecithin cholesterol acyltransferase promotes the uptake of free cholesterol by HDL by a reaction called esterification.

Hyperlipidaemia

- Hyperlipidaemia refers to an abnormality in the lipid profile, encompassing a variety of disorders relating to elevations in total cholesterol, LDL or TG, or conversely, lower levels of HDL.

- Primary hyperlipidaemia refers to a genetic defect in the lipid metabolism as a cause of the problem. For example, familial hypercholesterolaemia is a cause of primary hyperlipidaemia. It is characterised by a genetic mutation, resulting in impaired clearance of LDL from the circulation due to lack of LDL receptors.
- Secondary hyperlipidaemia refers to hyperlipidaemia secondary to a cause other than the genetic defect.

Causes

Primary hyperlipidaemia (genetic)	Secondary hyperlipidaemia
	• Diet rich in saturated fat • Sedentary lifestyle • Diabetes mellitus • Cushing's syndrome • Hypothyroidism • Nephrotic syndrome • Alcohol intake • Obstructive liver disease • Drugs (thiazide diuretics, steroids, oestrogens, protease inhibitors)

Management Strategies

- Lipid profile of a person is always interpreted with the risk factors for CAD that he/she may have as these may modify the LDL levels to be achieved.

Risk Factors that Modify LDL Goals

Positive risk factors
- Age (males ≥45 years; females >55 years)
- Low HDL cholesterol (<40 mg/dL)
- Smoking
- Hypertension (with or without treatment)
- Family history of premature CAD (at the age of <55 years in males and <65 years in females)

Negative risk factors
- High HDL cholesterol (>60 mg/Dl)*

*Presence of this negative risk factor negates one risk factor from positive risk factors category for calculation of overall risk to the patient

- The major five risk factors (age, total cholesterol, HDL cholesterol, smoking and hypertension) are considered to calculate a score known as Framingham Risk Score (FRS). It gives the risk of a person developing a cardiac event in the next 10 years.
- There are a few emerging risk factors not included in the list of major CAD risk factors that may contribute to the risk of CAD. These include:
  - Apolipoprotein B.
  - Lipoprotein(a).
  - C-reactive protein.
  - Hyperhomocysteinaemia.
  - Small, dense LDL particles.

Coronary Artery Disease (CAD) Equivalents
- These include:
  - Patients with diabetes.
  - Patients with FRS ≥20%.
- In patients with CAD equivalents, the goals of therapy are same as those for patients with established CAD. Previous guidelines were based LDL-C goals in various categories (as shown in the box on next page).

LDL Cholesterol Goals in Different Categories

Risk category	LDL goal	LDL level at which to initiate lifestyle modifications	LDL level at which to consider drugs
• CAD or CAD equivalent	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (optional below 130 mg/dL)
• 2 or more risk factors but no CAD	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
• 0–1 risk factor	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (optional between 160 and 189 mg/dL)

- In patients with acute coronary syndrome, stable CAD plus diabetes or rapid progression of atherosclerosis, the goal for LDL is below 70 mg/dL.

New Guidelines on Use of Statins

- The new guidelines do not give an absolute value of cut-off for reducing LDL cholesterol.
- Statins should be used for the prevention of atherosclerotic cardiovascular disease (ASCVD) in many individuals with higher risk of ASCVD for primary prevention and in all individuals for secondary prevention. No recommendations have been made for those who have NYHA class II-IV heart failure and who are receiving haemodialysis.
- Statin therapy reduces ASCVD events across the spectrum of baseline LDL-C levels ≥70 mg/dL. The groups include the following:
  1. Individuals with clinical ASCVD (acute coronary syndromes or a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin).
     - Patients <75 years require high-intensity statin therapy (i.e. daily dose of statin lowers LDL-C by approximately ≥50%).
     - If age >75 years, initiate moderate-intensity statin therapy (i.e. daily dose lowers LDL-C by approximately 30% to <50%).
  2. Individuals with primary elevations of LDL-C ≥190 mg/dL
     - Require high-intensity statin therapy (i.e. daily dose of statin lowers LDL-C by approximately ≥50%).
  3. Individuals with diabetes aged 40–75 years with LDL-C 70 to189 mg/dL and without clinical ASCVD.
     - Initiate moderate-intensity statin therapy (i.e. daily dose lowers LDL-C by approximately 30% to <50%) unless 10-year risk of ASCVD ≥7.5% where high-intensity statin therapy is required.
  4. Individuals with no clinical ASCVD or diabetes with LDL-C 70 to189 mg/dL and estimated 10-year ASCVD (non-fatal MI, CAD death, nonfatal and fatal stroke) risk >7.5% as calculated by Pooled Cohort Equations. If it is <7.5%, re-calculate the risk every 4-6 years.
     - Require moderate-to-high intensity statin therapy if age 40–75 years.
     - Benefits less clear in other age groups.

Note:
1. If patient has characteristics predisposing to statin-associated adverse effects or drug-drug interactions is a strong possibility, moderate-intensity statin therapy may be used instead of high-intensity therapy.
2. High-intensity statin therapy indicates use of atorvastatin 40-80 mg or rosuvastatin 20–40 mg/day. Medium-intensity statin therapy means atorvastatin 10–20 mg, rosuvastatin 5–10 mg, simvastatin 20-40 mg, pravastatin 40–80 mg, pitavastatin 2-4 mg and lovastatin 40 mg.
3. If response to statins is less than anticipated or patients are unable to tolerate a less than recommended intensity of a statin, or who are completely statin intolerant, consider addition of a non-statin cholesterol-lowering therapy using other medicines. However, these additional drugs may not reduce risk of ASCVD further.
4. Pooled Cohort Equations based on age, sex, race, total cholesterol, HDL cholesterol, systolic blood pressure, use of antihypertensive drugs, presence of diabetes and smoking history.

Management

Therapeutic Lifestyle Changes

- Reduced intake of saturated fats (<7% of total calories) and cholesterol (<200 mg/day). Saturated fats (cheese, milk and red meat) are replaced with monounsaturated fats (olive oil, canola oil) and polyunsaturated fats (corn oil, peanut oil). Monounsaturated and polyunsaturated fats should constitute up to 10% and 20% of total calories respectively.

- Increased intake of soluble fibre (10–25 g/day).
- Weight reduction, if overweight or obese.
- Increased physical activity, practically every day.
- These should be tried for 12 weeks before considering the use of drugs.

Pharmacotherapy

- This is used along with therapeutic lifestyle changes.
- First-line pharmacotherapy is the use of statins.
- If the patient is not able to tolerate a statin, a bile acid resin, fibrate or niacin is offered as a substitute.
- Benefits of drug therapy should initially be monitored at 6-week intervals. Once LDL levels are within recommended range, monitoring should be done every 6–12 months.

Statins or HMG-Coa Reductase Inhibitors

- This group includes simvastatin, atorvastatin, lovastatin, pravastatin, pitavastatin and rosuvastatin.
- This group of drugs inhibits the rate-limiting step in hepatic cholesterol synthesis, i.e. the conversion of HMG-CoA to mevalonate. These drugs also increase LDL receptor levels in hepatocytes and enhance clearance of LDL from circulation.
- These agents reduce LDL by 25–40%.
- Side effects:
  - Mild transient elevation of liver enzymes common but elevation of serum aminotransferases to more than three times the upper limits of normal occurs in less than 2% of patients. In these patients, therapy should be discontinued.
  - Another rare but serious side effect is the occurrence of myopathy manifested by muscle pain and elevation of serum muscle enzymes. This occurs in less than 1% cases, but is more common when statins are combined with fibrates, niacin or cyclosporin.

Factors Increasing Risk of Statin-Induced Myopathy

- Major illness
  - Severe infection
  - Surgery
  - Trauma
  - Hypoxia
  - Hypothermia
  - Uncontrolled seizures
- Chronic illness
  - Debilitation
  - Chronic renal or liver failure
- Endocrine and metabolic disorders
  - Hypothyroidism
  - Hyponatraemia
  - Metabolic acidosis
	- Medications (inhibit CYP3A4)
	  - Fibrates (gemfibrozil more than fenofibrate)
	  - Macrolide antibiotics
	  - Azole antifungals
	  - Calcium channel blockers (verapamil, diltiazem)
	  - Antidepressants (fluoxetine, fluvoxamine)
	  - Warfarin
	  - Cyclosporin
	- Viral infection
	- Others
	  - Concomitant use of recreational drugs
	  - Dose of statin

Bile Acid Sequestrants

- The oldest bile acid sequestrants are cholestyramine and colestipol.
- These agents interfere with the absorption of bile acids from the gut resulting in a compensatory increase in bile acid synthesis.
- The major effect of the bile acid sequestrants is to reduce LDL by 15–30%, with only modest changes in HDL.
- Side effects.
  - The major side effects are gastrointestinal (GI) distress and decreased absorption of other drugs.
  - These agents elevate TG level; elevated TG (>400 mg/dL) is a contraindication for this class of drugs.

Niacin

- It lowers LDL by 5–25%. It also significantly lowers TG and raises HDL.
- Side effects:
  - These include flushing, increased blood sugar and uric acid, and GI distress.
  - Its use should be avoided in people who have peptic ulcer disease or a history of gout.

Fibrates

- Gemfibrozil and fenofibrate are able to lower TG and modestly lower LDL. Typically, HDL increases by 10–15%.
- Side effects:
  - The side effects are mainly restricted to GI disturbance, and these agents should not be used in people with marked hepatic disease.
  - Other side effects include increase in gallstone formation and, rarely, myopathy.

Ezetimibe

- Ezetimibe localises at the brush border of the small intestine and inhibits the absorption of cholesterol from the diet.
- Specifically, it appears to bind to a critical mediator of cholesterol absorption, the Niemann–Pick C1-Like 1 (NPC1L1) protein on the gastrointestinal tract epithelial cells as well as in hepatocytes.
- In addition to this direct effect, decreased cholesterol absorption leads to an increase in LDL-cholesterol uptake into cells, thus decreasing levels in the blood plasma.
- Side effects.
  - Headache, diarrhoea; rarely elevated liver enzymes and myopathy.

Omega-3 Fatty Acid

- Useful to reduce TG levels.
- Dose is 1–2 g/day.

Newer Agents

- Torcetrapib is a cholesteryl ester transfer protein (CETP) inhibitors. CETP is a lipid transfer protein that is secreted by the liver and binds primarily to HDL, greatly facilitating the transfer of cholesteryl esters from HDL to apo-B-containing particles such as VLDL, LDL and chylomicrons, in exchange for TG. When CETP is inhibited HDL-C levels rise markedly. However, one recent trial was halted due to excess number of deaths in torcetrapib group.
- Lomitapide, a microsomal triglyceride transfer protein inhibitor is approved for use in adults with homozygous familial hypercholesterolaemia.

Main Effects and Side Effects of Drugs Used in Treating Hyperlipidaemia

Agents	Effects on LDL	Effects on HDL	Effects on TG
• Statins	↓↓↓↓	↑	↓↓
• Bile acid resins	↓↓↓	±	None
• Fibrates	↓	↑↑	↓↓↓↓
• Niacin	↓↓	↑↑↑	↓↓↓
• Ezetimibe	↓↓	None	None

Doses of Drugs Used in Hyperlipidaemia

• Statins	
• Simvastatin	20–80 mg/day
• Atorvastatin	10–80 mg/day
• Lovastatin	20–80 mg/day
• Pravastatin	10–40 mg/day
• Rosuvastatin	5–40 mg/day
• Pitavastatin	2–4 mg/day
• Bile acid resins	
• Cholestyramine	4–16 g/day in divided doses
• Colestipol	5–30 g/day in divided doses
• Fibrates	
• Gemfibrozil	600 mg twice a day
• Fenofibrate	200 mg/day
• Niacin	1.5–3.0 g/day
• Ezetimibe	5–20 mg/day
• Omega-3 fatty acids	2–4 g/day

Treatment of Hypertriglyceridaemia

Serum level of TGs	Treatment
• <150 mg/dL (normal)	None
• 150–199 mg/dL (borderline high)	Weight reduction, physical activity and dietary therapy Monitor and achieve LDL goals
• 200–499 mg/dL (high)	Weight reduction, physical activity and dietary therapy Monitor and achieve LDL goals Use drug therapy after achieving LDL goals
• >500 mg/dL (very high)	Weight reduction, physical activity and dietary therapy Drug therapy to lower TGs and then LDL lowering

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MEDICINE

Prep Manual for Undergraduates

Fifth Edition

The fifth edition of this book is a must-have for all undergraduate medical students as it prepares them for both theory and viva-voce examinations. It is also useful for dentistry and nursing students. Structured in question-answer format, this book presents a concise exam-oriented text as per the guidelines of Medical Council of India and Health Universities across the country.

Salient Features

- To the point presentation of text in question-answer format helps in quick revision before examination
- Topics presented in points with suitable boxes, tables, flowcharts and diagrams to facilitate easy understanding and revision
- Extensively revised, updated, and strengthened to keep up with the latest changes in the field of medicine
- Topics revised thoroughly like anaemia of critical illness, leukaemias and lymphomas, multiple myeloma, respiratory failure, tuberculosis, diffuse alveolar haemorrhage, pleural effusion, stroke, hypertension, acute coronary syndromes, ischaemic colitis, Behcet's disease, snake bites, hypothermia, vitamin D in health and diseases, hyperlipidaemias, H1N1 influenza, human immunodeficiency infection, approach to acid–base analysis
- New topics include dengue infection, sepsis bundles, chronic kidney disease, infectious diseases, obesity
- Inclusion of clinical decision pathways for some of the commonly encountered critical and non-emergent disease conditions
- Inclusion of newer innovations and treatments modalities

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